Body Integrity Identity Disorder (BIID):

A neuroscientific account of the desire for healthy limb amputation

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Abstract

Individuals with Body Integrity Identity Disorder (BIID) have the strong feeling that one or more healthy limbs do not belong to their body. Due to the incongruity between physical and perceived body they desire amputation of the non-belonging, unwanted limb(s). This desire for amputation constitutes a source of serious suffering. Currently, there is no consistent opinion about the underlying causes of BIID, and potential treatment options are controversially discussed. The general purpose of the present thesis was to investigate the neurological, neuropsychological and psychiatric characteristics of BIID. Specifically, we hypothesized that the unwanted limb is misrepresented in the brain and/or that the integration of multisensory information about the unwanted limb(s) may be disrupted at some processing stage. A series of behavioral experiments and a structural neuroimaging investigation were planned to address this hypothetical limb representational deficit.

The investigation comprised three standardized clinical examinations (neuropsychological, neurological and psychiatric), five behavioral experiments *(mental limb rotation, body transformation and task switching, rubber foot illusion, caloric vestibular stimulation and tactile temporal order judgments (TOJ))* as well as magnetic resonance imaging (MRI) in 15 individuals with BIID and 15 paired-matched control subjects.

Neurological, neuropsychological and psychiatric exams revealed normal functions in persons with BIID. While we failed to accumulate evidence for limb representational deficits in BIID in four behavioral experiments, a fifth experiment (TOJ) uncovered a disturbed spatio-temporal integration of tactile information in the unwanted compared to the accepted body part. The MRI investigation revealed gray matter morphological differences in circumscribed brain areas (right superior parietal lobule (SPL), right primary and secondary somatosensory cortex (SI and SII), right anterior insular cortex and both putamina) between the two participant groups.

We conclude that (1) BIID occurs in neurologically, psychiatrically and neuropsychologically grossly healthy persons, (2) tactile information from unwanted compared to accepted body parts is differently integrated at higher-order areas of body representation and (3) observed gray matter characteristics in persons with BIID may constitute a correlate of altered processing both at low-level stages (diminished limb representation in SI, SII and putamen) and higher-order stages of multisensory integration (defective "binding" of a body part into a coherent whole-body representation in the SPL and altered emotional connotations in the anterior insula). Together, the findings of the present thesis present evidence for an altered neuroanatomy in persons with BIID, which may lead to the feeling of non-belonging of the unwanted limb. This evidence should free the condition from its apparent bizarreness and from psychiatric mystifications.

Zusammenfassung

Personen mit Body Integrity Identity Disorder (BIID) haben das intensive Gefühl, dass eine oder mehrere Gliedmassen nicht zu ihrem Körper gehören. Aufgrund der Nicht-Übereinstimmung zwischen physischer und empfundener Körperform wünschen sie eine Amputation der ungewollten Gliedmasse. Der Wunsch nach Amputation wird als starke psychische Belastung erlebt. Gegenwärtig gibt es keine übereinstimmende Meinung über die Ursachen, die BIID zugrunde liegen und potentielle Behandlungsmethoden werden kontrovers diskutiert. Ziel der vorliegenden Dissertation war es, neurologische, neuropsychologische und psychiatrische Merkmale von BIID zu untersuchen. Im Besonderen nehmen wir an, dass die ungewollten Gliedmassen mangelhaft im Gehirn repräsentiert sind. Mit einer Reihe von Verhaltensexperimenten sowie struktureller Bildgebung des Gehirns (Magnetresonanztomographie, MRT) wollten wir dieses hypothetische Defizit der Gliedmassen-Repräsentations prüfen.

Die Studie bestand aus drei standardisierten klinischen Untersuchungen (neuropsychologisch, neurologisch und psychiatrisch), fünf Verhaltensexperimenten *(Mentale Rotation von Gliedmassen, Körpertransformation und Aufgaben-Umstellfähigkeit, Gummifuss-Illusion, kalorisch-vestibuläre Stimulation und taktile Stimulation für die Beurteilung zeitlicher Abfolgen)* sowie einer MRT Untersuchung bei 15 Personen mit BIID und 15 paarweise zugeordneten Kontrollprobanden.

In den klinischen Standarduntersuchungen ergaben sich unauffällige Funktionen bei Personen mit BIID. Während sich in vier Verhaltensexperimenten keine Hinweise auf ein Defizit der Gliedmassen-Repräsentation zeigten, konnte eine gestörte räumlich-zeitliche Integration von taktiler Information auf der ungewollten im Vergleich zur akzeptierten Gliedmasse entdeckt werden. Die MRT Untersuchung ergab Gruppenunterschiede in umschriebenen Arealen der grauen Substanz (rechter superiorer Parietallappen (SPL), rechter primärer und sekundärer somatosensorischer Kortex (SI und SII), rechte anteriore Insel sowie beide Putamina).

Wir schliessen daraus, dass (1) BIID in neurologisch, psychiatrisch und neuropsychologisch gesunden Personen vorkommt, dass (2) taktile Stimulation der ungewollten verglichen zur akzeptierten Gliedmasse fehlerhaft integriert wird, was einem Verarbeitungsdefizit auf höherem Integrationsniveau entspricht und dass (3) die beobachteten Unterschiede in der

grauen Substanz ein Korrelat von veränderten Funktionen sein könnten, welche einfachere Verarbeitungsstufen (verminderte Gliedmassen-Repräsentation in SI, SII und Putamen) wie auch komplexere Verarbeitungsstufen von multisensorischer Information betreffen (fehlerhafte Ganz-Körper-Repräsentation im SPL und veränderte emotionale Besetzung in der anterioren Insel). Zusammen weisen die Ergebnisse der vorliegenden Dissertation auf eine veränderte Neuroanatomie in Personen mit BIID hin, welche zum Gefühl der Nicht-Zugehörigkeit der ungewollten Gliedmasse führen mag. Diese Befunde sollten helfen, BIID den Stempel des Absonderlichen zu nehmen und vor einer voreiligen Psychiatrisierung zu schützen.

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Abbreviations

AIC	Anterior insular cortex
BID	Body image disorders
BI	Body incongruity
BIID	Body integrity identity disorder
BDD	Body dysmorphic disorder
CVS	Caloric vestibular stimulation
D-KEFS	Delis-Kaplan executive function
DTI	Diffusion tensor imaging
fMRI	Functional magnetic resonance imaging
GI	Gender incongruity
GID	Gender identity disorder
JND	Just noticeable difference
L	Left
LPS	Leistungsprüfungssystem
MEG	Magnetencephalography
MNI	Montreal neurological institute
MOLA	Medial-over-lateral advantage
MRI	Magnetic resonance imaging
OBT	Out of body transformation
OCI	Obsessive-compulsive inventory
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
OP	Parietal operculum
PSS	Points of subjective simultaneity
R	Right
RCFT	Rey complex figure and recognition trial
RFI	Rubber foot illusion
RHI	Rubber hand illusion
RTs	Reaction times
RWT	Regensburger Wortflüssigkeits-Test
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex

SBM	Surface-based morphometry
SCR	Skin conductance response
SD	Standard deviation
SOA	Stimulus onset asynchrony
SPL	Superior parietal lobe
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TOJ	Temporal order judgments
TPJ	Temporal parietal junction
VLMT	Verbal learning and memory test
WMS	Wechsler memory scale

1

General Introduction

1.1 Corporeal awareness

The human body is a material object, filling out a well-defined, finite volume of space. It is a very special "piece of space", one that we own and move, one that is always present and that separates us from all things around us (Vitacco et al., 2009). Thus, we perceive our body and others' bodies, for instance, through somatosensory and visual input, by a perfectly related interplay between motor intention and motor execution, by continuous feedback about motor actions, as well as by general knowledge about the behavior of bodies and by body-related emotions. In the brain these different aspects of information are dynamically integrated in various brain areas indirectly connected circuits and ultimately result in a global "experience of our body". The associated mental construct is called corporeal awareness (Berlucchi & Aglioti, 1997, 2010).

Researchers' attempts to decompose the term "*corporeal awareness*" have led to the characterization of two distinct terms, "*body schema*" and "*body image*". They are supposed to represent distinct types of brain mechanisms. The term "body schema" comprises the sensorimotor body representations involved in action and interaction with the environment (e.g., jumping over an obstacle or reaching for a pen). In contrast, the term "body image" groups all other representations about the body that are not used for action. For instance, the sense of body ownership (e.g., this index finger belongs to me), lexical-semantic knowledge about the body (e.g., this part of my body is my right thumb) or emotional attitudes toward one's own body (e.g., I feel pretty; Berlucchi & Aglioti, 1997, 2010; de Vignemont, 2010; Gallagher, 2005; Schwoebel & Coslett, 2005). However, the terms "body schema" and "body image" are differently and inconsistently used in the literature (Critchley, 1979). Moreover, Berlucchi and Aglioti (2010) highlight that the brain mechanisms underlying these two terms are in most cases not independent, but overlapping in a large extent. They therefore suggest giving up these two terms and to focus on multiple cortical distributed networks processing "many bodies in the brain".

These "bodies in the brain" can be disrupted in several illnesses. Whereas healthy persons usually have a one-to-one correspondence between the actual physical "blood-and-flesh" body and corporeal awareness, this correspondence can be interrupted in many disorders or special conditions (Vitacco et al, 2009; for comprehensive overviews see de Vignemont, 2010 and Giummarra et al, 2008). For instance, amputees, who lack a limb (e.g., arm is not physically existing any more) do nevertheless experience a specific awareness of its phenomenal persistence. Although amputees know for sure that their physical body ends at the point where the limb was severed, they vividly experience the presence of a limb "out there" (*phantom limb)*, protruding from the stump. That is an "animated piece" of extracorporeal space. Moreover, paraplegic patients, with a fully present, but partially dysfunctional physical body, may feel discrepancies between phantom sensations and the physical body. So, these patients may feel their legs in a position not corresponding to the one they actually take. These postural illusions may only be corrected by visual observation of the immobile legs. Furthermore, individuals born with a physically incomplete body – *amelia* or *dysmelia* – may in rare cases experience phantoms sensations of their congenitally absent or deformed limbs (Melzack et al., 1997). Hence, they experience themselves as "complete" and we conclude that the missing limb may be represented in the subject’s brain (Brugger et al., 2000; Hilti & Brugger, 2010; Price, 2006, for overview). Neurological patients with lesions in specific brain regions and a physically present, but not necessarily functional body may also face an altered correspondence between the actual physical body ("blood-and-flesh") and their felt body, their corporeal awareness. Some of these patients may claim to have multiple sets of arms or legs (*supernumerary phantoms*; Khateb, et al., 2009; Vuilleumier et al., 1997), whereas others report that their body has ceased to exist (*asomatognosia*; Arzy et al., 2006; Dieguez et al., 2007; Feinberg et al., 2009). Still other neurological patients are convinced that their densely hemiplegic body half is fully functional (*anosognosia*; Vuilleumier, 2004) or that they do no longer "own" these paralyzed parts (*somatoparaphrenia*; Bottini et al., 2002; Gerstmann, 1942; Vallar & Ronchi, 2009, for an extensive overview). Other neurological groups may feel attacked by their own, apparently "disowned" limbs (*anarchic limb phenomenon*; Marchetti & della Sala, 1998) or, conversely, may attack their own limbs (*misoplegia*; Critchley, 1974; Loetscher et al., 2006). Finally, in psychiatric patients, the interaction between the fully functional physical body and its corporeal awareness seems to be altered. For instance, patients with *body dysmorphic disorder* (BDD) are overly concerned about a perceived (but objectively non existing) defect of their physical body (Koran et al., 2008) and persons with *gender identity disorder* (GID), feel that their body's sex does not correspond with their experienced gender (Bostwick & Martin, 2007).

1.2 Body Integrity Identity Disorder (BIID)

There is another condition, where there is no one-to-one correspondence between the actual physical body and the way it is experienced. This condition is labeled *body integrity identity disorder* (BIID, term coined by First, 2005). In contrast to the above well-studied diseases, BIID is underinvestigated and its nature is entirely obscure. Over the past years, there were only a few studies examining the characteristics of BIID (e.g., Blanke et al., 2009; First, 2005; Hilti & Brugger, 2010; Kasten, 2009).

1.2.1 Description and characteristics of BIID

In BIID, the ordinary experience of the body as a whole is disturbed. Individuals with BIID have the strong perception that one or more healthy limbs do not belong to their body, even if the limb is physically and functionally normal. Thus, they experience an incongruity between the physical and their perceived body. They feel themselves as "overcomplete". They actually would feel as more complete without the unwanted limb (Blanke et al., 2009; First, 2005). In this respect, BIID is the mirror image of phantom sensations of congenitally absent limbs briefly described in the previous paragraph (Brugger et al., 2000; Hilti & Brugger, 2010). In BIID, a physically fully developed limb lacks any attributes beyond those of "blood-and-flesh" (an "incarnation without animation"), in contrast, the rarely experienced phantom sensations in people with congenital absent limbs may be conceptualized as the animation of a limb that has never been physically developed ("incarnated").

The prevalence of BIID is unknown, but estimates to point to several thousand individuals worldwide (Bayne & Levy, 2005). There is a clear predominance of men. The condition is not yet listed in a diagnostic classification manual (e.g., ICD-10 or DSM-IV-TR), however it is likely to appear in 2013 (Kasten, personal communication, March 2011) (characteristics of BIID see table 1).

To match their physical body to their corporeal awareness, people with BIID have a longstanding and enduring desire to have the unwanted limbs amputated (in order "to restore the true bodily identity"; First, 2005, p. 923). Individuals with BIID are entirely aware of the bizarreness of their amputation desire. Mostly, this desire is present since childhood or early puberty and remains stable over the years. Many individuals actually feel or exactly know where the amputation should be done (e.g., in the middle of the thigh). Regarding this desired location of amputation, the following phenomenological regularities in the largest two studies were found. In most cases the amputation desire concerns a major limb (e.g., concerns the whole lower leg and not only a single toe) on one or both body sides (Blanke et al., 2009; First, 2005). In 55% (Blanke et al., 2009) to 88% (First, 2005) of the individuals with BIID a unilateral limb amputation desire is apparent. Moreover, in 55% (First, 2005) to 64% (Blanke et al., 2009) of these unilateral amputation desires the left body side is more frequently affected than the right body side. Furthermore, legs (from 80% to 84%) as opposed to arms, as well as above-the-knee (from 70% to 92%) as opposed to below-the-knee amputees are predominantly the target of the amputation desire (Blanke et al., 2009; First, 2005).

Some individuals with BIID reduce their suffering by realizing the amputation of the unwanted limb. Even though such amputations of healthy limbs are not legal, a minority of persons with BIID find a surgeon to do it or they try to conduct self-amputations. The realization of the amputation is reported to extinguish the individual's amputation desire and to improve the individual's functioning (Braam & de Boer-Kreeft, 2009; First, 2005). So far, systematic pre- and post-amputation studies are lacking. Medical ethic debates concerning the amputation desire can be found in the periodical *American Journal of Bioethics* (Volume 9, issue 11) or in Mueller (2008). To reduce suffering in daily life a considerable number of people with BIID move and behave, as if they were amputated, e.g., by using wheelchairs or crutches. This practice, named *pretending*, can help to cope with the suffering. However, the satisfaction gained from this short-term activity may, in the long term, often reinforce and intensify the desire for amputation (Thiel et al., 2009).

What do we know about the mental health of individuals with BIID from a clinical point of view? The psychiatrist Michael First (2005) carried out the first large interview study with 52 participants with BIID. Of them, the majority had no psychiatric symptoms (except some mild depression or anxiety symptoms) and only an unremarkable co-morbid psychopathology. In line with these findings, Thiel et al., (2009) revealed ordinary personality and psychiatric profiles in another sample of 30 people with BIID. It is important to mention that the desire of amputation in individuals with BIID differs from the delusional beliefs with an accompanying urge to perform self-mutilations, such as occurring in schizophrenia. (e.g., Large et al., 2009).

Furthermore, BIID is also distinct from the psychiatric disease of body dismorphic disorder (BDD), because individuals with BIID do not experience their unwanted limb as being exceptionally ugly or unpleasant (Thiel et al., 2009). The respective authors found slight tendencies for narcism (e.g., an enhanced need to be special) and a slight trend towards obsessive compulsive behavior (e.g., recurrent and persistent thoughts or impulses) in individuals with BIID. In sum, research has so far not found any evidence for psychiatric illnesses in BIID. However, specific slightly enhanced psychological or psychiatric patterns cannot be ruled out to go along with the disorder.

A further characteristic of BIID is its sexual components (First, 2005; see chapter 2.1.1). They are expressed in feeling sexually attracted to amputees (*acrotomophilia*; Money & Simcoe, 1984/1986) or in being sexually aroused by imagining oneself being an amputee (*apotemnophilia*; Money et al., 1977). Fifteen percent of individuals with BIID (First, 2005) reported that their sexual motivation was their primary reason for their amputate desire. Fifty-two percent of the individuals with BIID rated the sexual motivation as their secondary reason for their amputation desire. Their primary reason for amputation desire (in 63% of participants) was "to restore the true bodily identity" (First, 2005, p. 923). The reasons for presence of a sexual component in BIID are so far unexplained.

Table 1: Tentative diagnostic criteria's of BIID (adapted from Ryan, 2009, according to Kasten, March 2011).

1. A strong and longstanding desire for the amputation of a limb. Commonly having persisting since childhood or adolescence.
2. The primary motivation for the desire is the feeling that being an amputee is one's true and proper identity. A substantial psychological distress is consecutive to the feeling that the real body does not match one's mental body of being an amputee. The concerned limb is perceived as not owned and less "animated" ("beseelt", in German), despite of normal sensory and motor function. Typically, a demarcation line between accepted and non-accepted part of the limb can be specified.
3. The desire for amputation bothers the affected individuals strongly and leads to psychological burdens. The desire is often bashfully hidden from social and occupational networks.
4. Affected people hope to extinguish the felt discrepancy by amputation or other therapies. Dangerous self-inflicted amputations can be realised.
5. The disorder is not better explained by another medical or psychiatric condition, as for example, body dysmorphic disorder or targeted self-injurious behavior.
6. Minor criteria: pretending, erotic or sexual attraction (feeling sexually attracted to amputees or being sexually aroused by imagining oneself an amputee)

1.2.2 Clinical treatment possibilities

So far, attempts of medical (e.g., psychotropic) or psychotherapeutic treatment did not lead to any noticeable alleviation of the amputation desire (Bayne & Levy, 2005; Braam et al., 2006). These treatments did only reduce depressive symptoms or guilt feelings in some individuals with BIID (First, 2005). Beside such treatments neuro-otological approach was supposed to reduce the amputation desire temporarily (Ramachandran & McGeoch, 2007b). This method is caloric vestibular stimulation. In patients with somatoparaphrenia, who experience their paralyzed limbs as disowned, caloric vestibular stimulation could temporarily restore body ownership (Bisiach et al., 1991). Therefore, the method may be helpful to alleviate the amputation desire in BIID for a short term.

1.2.3. Causes of BIID

What could be the causes of BIID? Until recently, BIID is sparsely investigated. In the limited scientific literature there is no consistent opinion about its underlying causes. Models for understanding BIID predominantly focus on neurological, psychological/psychiatric and biographical components. This integrative approach seems to accommodate the complexity of BIID best (Giummarra et al., 2011), because one single perspective is unlikely to sufficiently explain its heterogeneity. Figure 1 displays an integrative model of BIID (modified after Oddo et al., 2009).

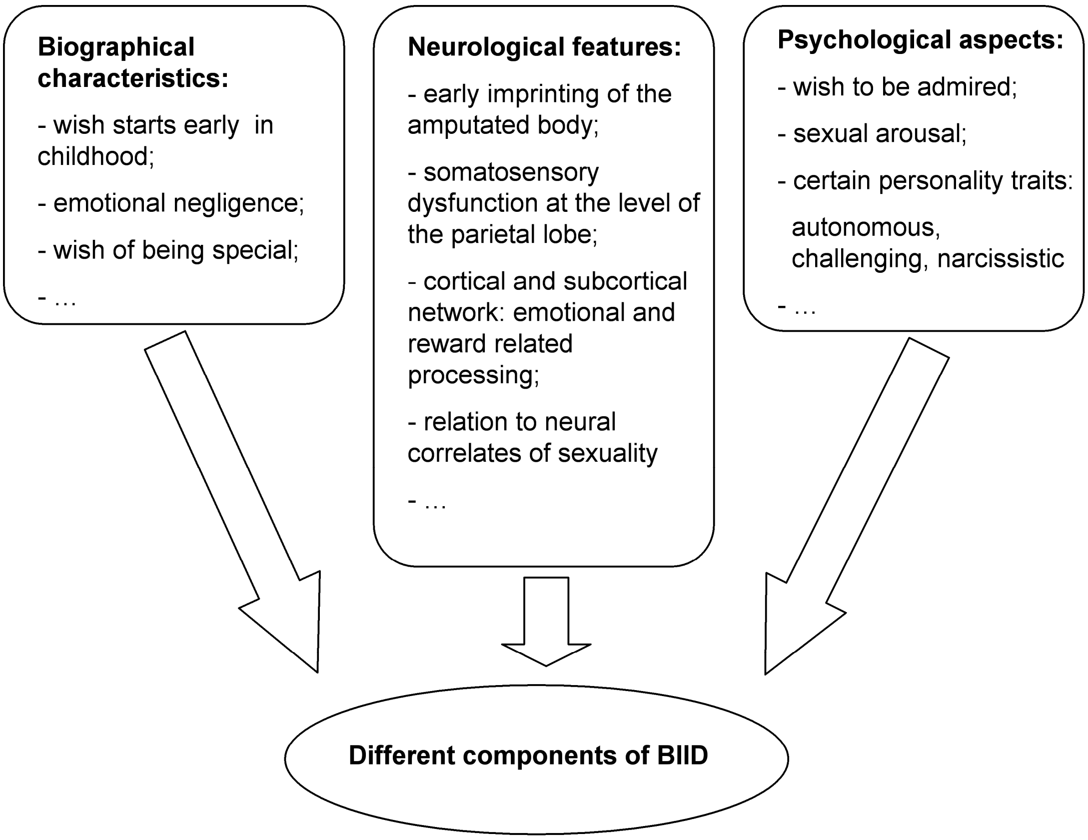


Figure 1. Different elements of BIID in an integrative model (after Oddo et al., 2009, p. 244).

Neurological account

Previous studies investigating the phenomenological characteristics in BIID (e.g., present since childhood or overrepresentation of left leg) point towards altered neurological body representations. Experimental studies that explore BIID from a neurological point of view have been communicated so far by two studies of the same research group (Brang et al., 2008; McGeoch et al., 2011). They proposed a dysfunction of the right parietal cortex, especially the superior parietal lobule (SPL) in individuals with BIID. In the literature it is proposed that the right SPL integrates multisensory information of connected brain areas (e.g., Giummarra et al., 2008; Lewis, 2006; Stein, 1989; Wolpert et al., 1998). In the first study, Brang et al. (2008) investigated two persons with BIID and found that that the felt pinpricks to unwanted body parts elicited an abnormally strong skin conductance response (SCR) in comparison to those to accepted body parts. SCR is an index of autonomic arousal, which is used as an objective measure of conscious and unconscious emotional processing and attention (Damasio, 1994; Frith & Allen, 1983; Ohman & Soares, 1993). Increased SCR has been associated with the right insula (Critchley et al., 2000). The authors speculated that the felt touches on the unwanted limb are normally processed in the somatosensory cortex, but not further integrated in the higher-order SPL, because the unwanted limb is somehow misrepresented in that region. This would lead to the discrepant feeling of not owning the critical limb, while still feeling the pinpricks. In the insula this discrepancy would finally lead to the observed, exaggerated SCR.

To test their hypothesis of the involvement of the parietal cortex in BIID, the same research group conducted a further empirical study using functional magnetoencephalography (MEG; McGeoch et al., 2011). Four participants with BIID, who had a left, right or bilateral limb amputation desire, were stimulated, e.g., touched on their unwanted and accepted foot during MEG. The subjects reported to feel the touches on both feet. The MEG results showed activation in the right superior parietal lobule (SPL) following stimulation on the accepted foot, however, significantly less activation was found following comparably strong stimulation on the unwanted foot. The authors suggested that people with BIID could feel the touch on their unwanted limb (perceived somatosensory signals), however without a proper representation of the specific limb in the SPL, felt touch would not "bind" it into a higher order body representation. The assumption of a dysfunctional right parietal lobe and connected networks implicated in the genesis of BIID is supported by several researchers (Blanke et al., 2009; Brugger 2007; Giummarra et al., 2011; Hilti & Brugger, 2010). Such an assumed disturbance in the SPL is suggested to have its beginnings during early ontogenetic development (e.g., Blanke et al., 2009; McGeoch et al., 2011).

Psychological / psychiatric account

The parietal lobe and associated networks might not be the only locus of interest in connection with BIID. There are observations in BIID that are not readily compatible with BIID as a neurological deficit in limb representation. Accordingly, some rare case studies document that the desire for amputation can switch from one to the other body side (Kasten, 2009; Kasten & Stirn, 2009). Another observation not readily compatible with the neurological account of BIID concerns those cases of the disorder, in which the amputation of a target limb is followed by a new amputation desire of a previously well-integrated limb (Berger et al., 2005; Sorene et al., 2006). Although rather atypical, these rare cases illustrate that there is still a need for a unifying theory of BIID, which accounts for the broad variability in individual symptoms (Hilti & Brugger, 2010).

From a psychological point of view it is proposed that changes of the amputation desire, as well as newly emerged amputation desires, could be explained by a general desire to reach disability (Baubet et al., 2007; Kasten, 2009; Thiel et al., 2009). The respective authors explain that such a disability desire could develop during sensitive phases in childhood when a child is in contact with an amputee who receives attention for his disability, while the child itself experiences emotional deprivation. However, imprinting contacts with amputees during childhood, without an associated deprived emotional state are also reported by several persons with BIID (Kasten, 2009; see own data in chapter 2.1.1, p. 19, table 3). Often such contacts are remembered as *eliciting events* in early childhood, which trigger explicit awareness of the amputation desire. However, in our opinion such incidents are unlikely to be a cause of the disorder. It rather appears that an early, prenatal failure in limb integration must have prevented a fully animated limb to develop in the first place (Blanke et al., 2009; Hilti & Brugger, 2010).

1.3 Linking BIID to gender identity disorder (GID)

In this last section, BIID will be compared to GID. GID, whose acronym has primed that of BIID, could provide insights into specific neurological and psychological characteristics of BIID. Various recent findings underline a possible etiological similarity between BIID and GID (for overview see Lawrence, 2006; Nieder & Richter-Appelt, 2009). (Note that GID will possibly be renamed GI, meaning *gender incongruity* (Lawrence, 2010). This could be the case for BIID as well (BI for *body incongruity*)). Both disorders may be subsumed under the umbrella term of *body image disorders* (BID) which brings them close to *body dysmorphic disorder* (BDD), *eating disorder* and the *somatoform disorders* (Cororve & Gleaves, 2001). The development of GID is thought to be a dynamic process relying on the interaction of biological and psychosocial factors (summarized in Nieder & Richter-Appelt, 2009). Very early alterations in body representation in the brain were suggested to be an underlying cause of GID (Ramachandran & McGeoch, 2007a). Apparently, the wish to change one's gender might be accompanied by an underrepresentation of gender-specific organs in the brain. Thus, fewer GID patients experience phantom penises after female-to-male reassignment surgery as compared to non-transsexual individuals with an involuntary penectomy. This observation, although largely anecdotal and based on a relatively small number of cases, justifies theoretical considerations that GID and BIID share specific similarities (Lawrence, 2006, 2010). Another possible similarity between GID and BIID is supposed to be obsessive compulsive behavior (e.g., Thiel et al., 2009). In GID, obsessive-compulsive disorder (OCD) is the most commonly reported comorbidity (Hepp et al., 2005; Neziroglu & Yaryura-Tobias, 1997). Therefore, the repetitive conviction in GID of belonging to the opposite sex and the suffering from the subsequent physical non-match, continuously experienced have much in common with obsessive compulsive symptoms. The same form of conviction, i.e., not filling out a body with a regular set of four limbs, is at the same heart of BIID. Accordingly, many persons with GID can't help cross-dressing, and many persons with BIID can barely resist the urge to "pretend" being an amputee. The views as outlined here open up a potentially fruitful collaboration between psychiatrists and neurologists.

1.4 Hypotheses of the doctoral thesis

The general purpose of my thesis was to explore the neurological and psychiatric components of BIID in more detail. This is the first extensive study that comprises clinical examinations, behavioral experiments and magnetic resonance imaging (MRI) investigations in a group of individuals with BIID. These examinations and experiments serve to investigate our leading hypothesis, that the unwanted limb is underrepresented in the brain of individual with BIID, based on the literature summarized above (e.g., Blanke et al., 2009; Hilti & Brugger, 2010; McGeoch et al., 2011)

In the present thesis we focused on persons with BIID with an amputation desire concerning their legs. It is important to mentioned that beside the desire for amputation of legs or arms, other variants of BIID are known, e.g., the desire to become a paraplegic (Bruno, 1997; Giummarra et al., in press). Thus, individuals with paraplegia-BIID are convinced that their normally functioning limbs should be paralyzed. Thus, throughout the thesis the term *BIID* means specifically the variant of *amputation* desire.

In our study, 15 individuals with BIID and 15 healthy control persons participated. Each subject took part in three clinical examinations (i.e., neuropsychological, neurological and psychiatric), in four or five behavioral experiments (i.e., mental rotation, body transformation and task switching, rubber foot illusion, caloric vestibular stimulation and temporal order judgments), as well as in structural MRI (see table 2). In the following sections the working hypotheses for each clinical examination, behavioral experiments and the MRI investigation are outlined.

Clinical examinations

In the *neuropsychological* examination (chapter 2.2.2), subjects were extensively evaluated in various cognitive domains (e.g., attention, memory and executive functions).

- We predicted normal cognitive function in participants with BIID. Except in cognitive switching, where we expected a reduced performance in those participants with BIID with marked obsessive-compulsive symptoms as revealed by the psychiatric examination.

In the standardized *neurological* examination (chapter 2.2.3) functions such as sensory detection, vibration or position sense were examined.

- No differences between the unwanted and accepted limb were expected (Brang et al., 2008; McGeoch et al., 2011).

In the extensive *psychiatric* examination (chapter 2.2.4) a structured clinical interview and several self-rating questionnaires were evaluated.

- We expected that the group with BIID might specifically show elevated obsessive compulsive symptom scores (Thiel et al., 2009), but not in other psychiatric characteristics (First, 2005).

Behavioral experiments

In our five behavioral experiments we predicted specific responses of the group with BIID to the undesired limb, while its normally integrated counterpart served as a within-subject control. In three experiments we especially analyzed data of homogenous subgroups with a left-sided leg amputation desire and right handedness/footedness to reduce statistical noise.

First, in the computerized *mental rotation task* (chapter 2.3.1), subjects had to decide whether a left or a right foot or hand was depicted.

- We predicted prolonged reaction times, in individuals with BIID, when they had to mentally rotate the depicted foot corresponding to their undesired limb. This would be due to a hypothetical underrepresentation of the leg in the brain (e.g., impaired integration of visuo-motor information) that may affect the ability of mental rotation (Funk & Brugger, 2008; Giummarra et al., under review a).

Second, in the computerized *body transformation and switching task* (chapter 2.3.2), subjects had to decide whether a depicted figure had a left or right leg amputation.

- We expected faster reaction times for those displays, which correspond to the desired amputation site, due to faster visual-motor integration, than when an incompatible stimulus-representation pairing would be shown.

Furthermore, the subjects had to respond to two different transformation types in different trials, in order to investigate their ability of cognitive switching.

- With respect to BIID, this ability was expected to be reduced in those individuals showing pronounced presence of obsessive compulsive symptoms (Thiel et al., 2009).

OCD is normally accompanied by such a reduced cognitive switching performance (Chamberlain et al., 2005, 2008; Head et al., 1989).

Third, in the *rubber foot illusion* experiment (RFI; chapter 2.3.3) subjects' unseen foot was stroked while they had to watch a rubber foot that was simultaneously stroked. This may elicit an illusion in feeling the rubber foot belonging to oneself (Botnivick & Cohen, 1998). The illusion was quantified by three measurements (see table 2).

- For persons with BIID we hypothesized a larger illusion (i.e., sense of ownership) for the rubber foot corresponding to their unwanted foot compared to that corresponding to the accepted foot. This would be due to a hypothetically altered integration of multisensory information concerning the critical foot.

Fourth, during the *caloric vestibular stimulation* (CVS; chapter 2.3.4), both ears were stimulated with cold water.

- We predicted that cold water CVS of the left ear temporarily alleviates the desire for limb amputation in BIID (Ramachandran & Mc Geoch, 2007b).

Fifth, in the *temporal order judgment* (TOJ; chapter 2.3.5), subject with BIID with a unilateral amputation desire had to rate which of two tactile stimuli was applied first. Stimulation was pairwise to proximal and distal sites of their desired amputation line.

- We predicted a differential temporal integration of touch at locations on "accepted" versus "unwanted" body sites. This method involves spatio-temporal integration, a process in which the parietal lobes are crucially involved (e.g., Pastor et al., 2004).

Table 2: Overview of the independent and dependent variables of the five behavioral experiments

Number	Chapter	Behavioral experiment	Independent variables	Dependent variables
1	2.3.1	Mental rotation	Limb, side/laterality, view, rotation angle	Reaction times and accuracy of correct decisions
2	2.3.2	Body transformation and task switching	Frequency, task, amputation side, view	Reaction times and accuracy of correct decisions
3	2.3.3	Rubber foot illusion	Left vs. right foot, synchronous vs. asynchronous stimulation	a) Perceived vividness, b) Proprioceptive drift, c) Skin temperature
4	2.3.4	Caloric vestibular stimulation	Stimulated ear, time point, side, limb	a) Rated feeling of disturbance, b) Skin temperature
5	2.3.5	Temporal order judgments	Across- limb conditions Within-limb conditions	Just noticeable difference, subjective simultaneity

Magnetic resonance imaging (MRI) investigation

Using surface-based morphometry (SBM; chapter 2.4.1) we delinated gray matter differences of cortical thickness, surface area and volume between individual with BIID and healthy controls. We focused on right parietal, insular and subcortical areas, known to process low- and high level information about body parts including the legs.

- We focused on differences in right parietal, insular and subcortical areas (Blanke et al., 2009; Brugger 2007; McGeoch et al., 2011) thought to process low- and high level information about legs including emotional connotations of limb ownership.

In the following chapter, the clinical examinations and the behavioral and imaging experiments are described in separate sections. Each section follows the structural division into the paragraphs *Introduction*, *Subjects*, *Design and Procedure*, *Data analysis*, *Results* and *Discussion*.

2

Experimental Part

2.1 Subjects

The 15 participants with BIID attending in the study were all men, with a mean age of 49.1 years ranging from 28 to 73 years (SD = 14.2). We also recruited 15 control persons, without the disorder and carefully matched to age, handedness/footedness and approximate years of education, with a mean age of 49.3 years, ranging from 28 to 73 years (SD = 13.2). Both groups underwent identical examination, i.e., each participant has been assessed clinically (extensive psychiatric, neurological and neuropsychological testing; see chapter 2.2), took part in four to five behavioral experiments (see chapter 2.3) and in the magnetic resonance imaging (MRI) examination (chapter 2.4) during 1.5 days. Exclusion criteria for all subjects were any clinically relevant abnormalities. Two participants with BIID could not be subject to MRI due to the presence of metallic implants or a too large head circumference, respectively. Participants were recruited via the internet via or via word of mouth (e.g., internet-based forums and websites for BIID) over a period of six months. This study was approved by the local ethics committee (Kantonale Ethikkomission Zürich) and all participants gave written informed consent.

2.1.1 BIID subjects

Characteristics of the individual BIID condition were carefully assessed by questionnaires and personal interviews.

Demographic details

All participants had German as their native language. The majority lived in Germany (n = 12; 80%), the others in Switzerland (n = 3; 20%). Participants were mostly well educated (mean years of education = 16.1, SD = 2.3), all participants had at least 12 years of schooling, 20% (n = 3) a college/bachelor degree and 53.3% (n = 8) a university or equivalent higher academic degree. Two participants were left-handed and left-footed; all others were right-handed and right-footed according to Chapman and Chapman (1987) and Coren (1993) The sexual orientation was described as heterosexual in 46.7% (n = 7), as homosexual in 40% (n = 6) and 13.3% (n = 2) told to be mainly sexually oriented to male amputees. Compared to the study of First (2005; 31% homosexual participants) the proportion of homosexual participants is higher in the present study.

Limbs desired for amputation

All participants desired a leg amputation, nine of the left leg (60%) and two of the right leg (13.3%). Three aimed at a bilateral leg amputation and one person had an amputation desire mainly for the left leg, but to a lesser extent, also of the right leg amputation (same amputation level). During the study none of the participants were leg amputated. Two participants aimed additionally an upper limb amputation, one of the left arm since he was a child and one of the right index finger for some years. The latter participant had already realized the finger amputation at the time of the study (self-inflicted).

The desired amputation area was specific in all participants. All wanted an above-knee amputation, four (26.7%) wanted to have a long stump with an amputation located some centimeters above the knee, eight participants (53.3 %) desired an amputation in the middle of the thigh, two (13.3 %) about 10-15 centimeters below the hip joint and one (6.7 %) could not further specify the area on his thighs because of changing perceptions. No other desires were reported (e.g., for other amputation or handicaps).

Unsuccessfully performed self-inflicted injuries to obtain an amputation were reported by three participants. Four participants reported having plans to gain an amputation. Half a year after the participation in the study one participant had removed his leg and told of a remarkable well-being with a fully lost of his amputation desire. Also his sexual interest in amputees had been disappeared.

Onset and course of amputation desire

All participants had their amputation desire since childhood, from very early on ('as long as I can remember') to an age of 10 years (except in one participant with an amputation desire emerging later, around puberty) (p. 19, table 3). Roughly one third reported "eliciting events" for their amputation, mostly imprinting exposures to the sight of amputees. The other third was unsure if their remembered exposures to amputees were fascinating experiences rather than a primarily eliciting cause of their amputation desire. Finally, the last third described no such consciously perceived eliciting moments.

The intensity of the amputation desire over life span was described as mostly progressive for 66.7% (n = 10), as variable over time for 20% (n = 3) and of constant for 13.3% (n = 2). The leg desired for amputation remained constant over life time in twelve participants (80 %). In contrast, three participants reported an unstable desire; in one the amputation desire targeted the left leg or both legs during study participation. A second participant described a changing amputation desire during childhood concerning different parts of all four limbs that gravitated in puberty forwards a right-leg amputation desire. A third participant depicted an amputation desire slowly changing from the right leg in childhood to a left-leg amputation desire stable since puberty, without remembering any details or causes of this transition.

Amputation as a treatment

Ninety percent of 20 persons with BIID (Blanke et al., 2009) considered amputation of the non-desired limb as the only way to bring about relieve from BIID. Also in our sample a high percentage of belief in amputation as the only treatment was found in response to the question: *"How large would you estimate the chance that your desire of amputation will have been permanently removed within the next 5 years, without realization of the amputation itself?"* Sixty percent of the participants (n = 9) assigned this event a zero probability, whereas forty percent (n = 6) estimated that the desire could vanish without an amputation, albeit with a low likelihood of 16%.

More insight into the predominating attitude towards amputation as today's best treatment, may give the following question: *"Suppose you had the choice between two highly reliable specialists, A and B. A could perform the amputation you desire without any adverse side-effects. B could take away your desire for amputation permanently. Leaving everything else as it is. Whom would you select?"* The large majority of the 15 participants chose specialist A, who would perform the amputation and not specialist B, who could take away the desire. A comparably high ratio we obtained in a larger sample of 38 persons with BIID answering the same question. Why they have chosen specialist A was explained in participants from both samples as follows: *After decades of suffering I am sure an amputation would remove the desire in the long run; I don't want to be another person* [in loosing my desire], *much as I don't want to take a pill against my homosexuality; After very long phases of life full of despair and worries about my mind, this desire meanwhile became a part of my every-day life and simply belongs to me; I prefer to be amputated then to be psychologically cured from BIID; I love to have stumps; I want to have a legless body; Prostheses belong to my personality, I don't want to loose my sexuality associated with stumps*. The minority that chose specialist B to take away the desire without amputation, explained their decision with more practical reasons, e.g., *life without two legs can be very difficult; My life quality would be limited,* or by ambivalent thoughts as *"B would be nice, but I would miss a part of my inner life, of my identity"*. Some of the participants reported difficulties to answer this question with a simple decision.

Table 3: Characteristics of the 15 participants with BIID and their amputation desire

Participant	Study Code	Age [years]	Handedness and Footedness	Amputation desire since age [years]	Undesired leg(s)	Triggering event	Mean scores on the Zurich BIID scale (SDs in brackets)			
							Subscale 'pure amputation desire' [max.=6]	Subscale 'erotic attraction' [max.=6]	Subscale 'pretending behavior' [max.=6]	Whole Score [max.=6]
#1	101	41	R / R	Age 8-10	Left	No	5.8 (0.5)	4.3 (2.4)	3.8 (2.6)	4.6 (1.7)
#2	102	46	R / R	Since I can remember	Left	Maybe, some incisive memories	4.0 (1.8)	5.3 (1.5)	4.3 (1.5)	4.5 (0.2)
#3	104	63	R / R	Approx. age 7	Left	Yes, admiration of male leg-amputee	5.5 (1.0)	2.5 (1.0)	4.0 (2.5)	4.0 (0.8)
#4	107	57	R / R	Age 6-8	Left	Yes, contact to amputees	5.5 (1.0)	3.8 (1.5)	3.8 (2.2)	4.3 (0.6)
#5	108	29	R / R	Age 4-5	Left	No	5.0 (1.4)	6.0 (0.0)	4.3 (2.2)	5.1 (1.1)
#6	109	28	R / R	Approx. age 7	Left	Yes female arm-and male leg-amputee	5.5 (1.0)	6.0 (0.0)	4.8 (2.5)	5.4 (1.3)
#7	111	44	R / R	Age 9	Left	No	5.8 (0.5)	3.3 (1.0)	4.0 (2.2)	4.3 (0.9)
#8	113	67	R / R	Age 8	Left	Yes, postman was arm amputated	5.5 (0.6)	5.8 (0.5)	3.8 (2.6)	5.0 (1.2)
#9	114	36	L / L	Approx. age 10	Left	No	5.5 (0.6)	6.0 (0.0)	4.5 (2.4)	5.3 (1.2)
#10	105	33	L / L	Age 8-10	Right	Maybe a male amputee	5.5 (1.0)	4.3 (1.0)	1.8 (1.0)	3.8 (0.0)
#11	115	56	R / R	Approx. age 10	Right	Yes, several impressions	4.3 (1.5)	4.5 (0.6)	1.8 (0.5)	3.5 (0.6)
#12	103	45	R / R	Approx. age 9	Both	No	5.8 (0.5)	5.0 (0.8)	4.0 (2.2)	4.9 (0.9)
#13	106	73	R / R	Since I can remember	Both (or Left)	Maybe, a male leg-amputee	4.8 (1.5)	6.0 (0.0)	3.5 (1.7)	4.8 (0.9)
#14	110	59	R / R	Approx. age 7	Both	Maybe, several contacts to amputees	5.5 (1.0)	5.0 (2.0)	4.5 (2.4)	5.0 (0.7)
#15	112	60	R / R	About early puberty	Both	Yes, several contacts to amputees	3.8 (2.6)	5.0 (1.2)	2.3 (1.9)	3.7 (0.7)

2.1.2 BIID Questionnaire (Zurich BIID Scale)

We compared our study sample of 15 participants with BIID with a larger sample of people with BIID from our internet questionnaire (n = 38) in evaluating 12 statements (Zurich BIID Scale; Aoyama et al., 2011, in press). The participant has to respond on a Likert-type scale from 1 (strongly agree) to 6 (strongly disagree). All items of the questionnaire (English translation) are listed below in table 4. Based on Bruno (1997) there are three subscales (‘pure amputation desire’, items 1,2,5,10; ‘erotic attraction’, items 3,6,9,12; ‘pretending behavior’, items 4,7,8,11), each with 4 items. In 2 of the 4 items of each subscale, the wording is such that "strongly agree" loads positively to the score and in the other 2 it loads negatively.

Mean scores on this questionnaire and its subscales are listed for each participant in table 3. As illustrated in figure 2, they did not differ from the scores of the sample of 38 individuals with BIID; whole scale (12 items): t(df = 51) = 1.9, p = .069; pure amputation desire: t(df = 51) = .70, p = .55; erotic attraction: t(df = 51) = 1.3, p = .21; pretending behavior: t(df = 51) = .84, p = .41. Items of the first subscale concerning the manifestation of the amputation desire (e.g., “My desire for amputation is so strong that it determines my life”), were expectedly rated in both groups as the highest on an average at 5.2 (SD = 0.7) for the smaller study sample, respectively at 5.0 (SD = 0.9) for the larger internet sample. Further, both groups rated the erotic attraction by an amputation (e.g., “If I were amputated, I would experience my body as more erotic”) as second highest at 4.8 (SD = 1.1), respectively at 4.4 (SD = 1.2) and pretending behavior (e.g., “I sometimes pretend (for myself or for others) to be amputated”) with lower ratings at 3.7 (SD = 1.0), respectively at 3.4 (SD = 0.9). Thus, both groups attributed the same relative importance to the major phenomenological manifestations of the disorder (Bruno, 1997), with overall higher ratings for the study sample (whole scale = 4.5, SD = 0.6) than for the larger internet sample (whole scale = 4.3, SD = 0.6).

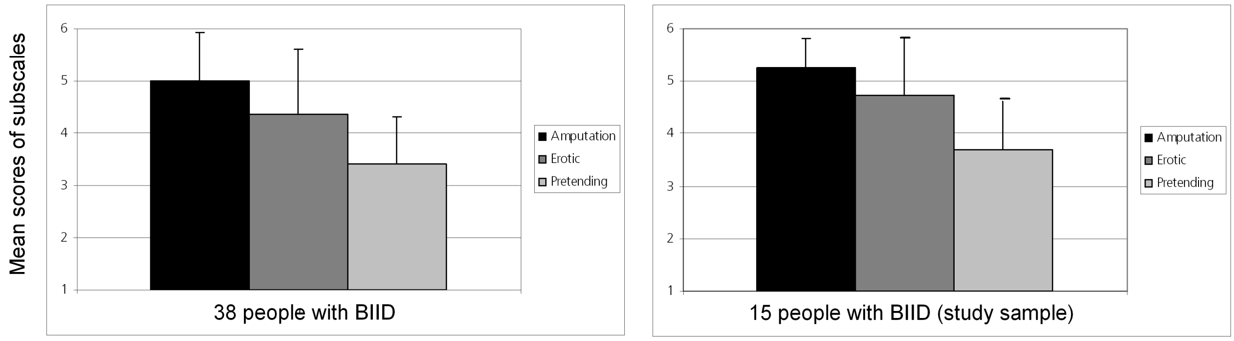


Figure 2: Mean scores on the three subscales of the Zurich BIID Scale for additional 38 people with BIID (left figure) and for the 15 study participants (right figure). The mean scores of the three subscales are depicted, including the 'amputation desire' (black), 'erotic attraction' (dark grey) and 'pretending behavior' (light grey). Error bars are standard errors of the mean.

Table 4:The 12-item Zurich BIID Scale

(1) My desire for amputation is so strong that it determines my life
(2) I have never played with the thought to amputate myself / to provoke an accident
(3) If I could choose between a sexual partner with an amputation and one without (everything else equal), I would go for the one without amputation
(4) I am far from moving and behaving as if I were amputated
(5) Despite the fact that I would have a body part removed, I would feel more "complete"after the desired amputation
(6) If I were amputated, I would experience myself as more erotic
(7) Instruments commonly used by amputees (prostheses, crutches, calipers, wheelchairs) do not fascinate me in any way
(8) I sometimes pretend (for myself or for others) to be amputated
(9) The theme of amputation plays an important role in my erotic fantasies
(10) However present, my desire for amputation is probably rather playful, i.e., a not-so-serious fantasy
(11) If I succeeded to make people around me believe that I am already amputated, it could reduce my desire for actual amputation
(12) For myself, the desire for amputation does not have any erotic or sexual connotation

2.2 Clinical Examination

2.2.1 Medical history

All subjects had an uneventful medical history, specifically normal child development (e.g., no known complications during pregnancy and birth or no supposed attention deficit disorder in childhood) or no serious medical or neurological illness. All, except one denied remarkable head injuries during their life. The exceptional participant reported a skull fracture that had occurred over twenty years ago and of which he fully recovered; subjectively fully regained health state (This subject's neuropsychological exam was normal, throughout). Past psychiatric disorders were reported by three participants with BIID (depression and anxiety, very likely due to suffering from BIID) and by two control participants (stress, burnout). In their first-degree relatives no remarkable neurological disorders (except two mothers with dementia disease) and psychiatric disorders (except one case of depression and suicide) were known. All participants denied a current substance abuse (except nicotine) and had no exceptional medication. Reduced concentration ability was currently complained by one person with BIID and two control persons. They considered work stress or difficult psychosocial situations as possible causing factors. Their attention function proved normal, however. No other complaints about the cognitive functioning were brought forward by any other participant.

2.2.2 Neuropsychology

In the neuropsychological assessment both groups were evaluated in various cognitive domains. Attention/cognitive speed was evaluated using the computer task *Go/Nogo* for selective attention from the test battery for attention TAP (Testbatterie zur Aufmerksamkeitsprüfung; Zimmermann & Fimm, 2007), as well as using two subtests for speed testing during color naming and reading from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001). In the executive functions the ability to control interferences and flexibility was examined verbally with D-KEFS (color-word interference respectively flexibility; a version of the *Stroop test* from Stroop, 1935) and nonverbally using the TAP tasks *Incompatibility* (stimulus-reaction incompatibility to presented arrows), respectively *Flexibility* (set shifting of figures). Spatial rotation was tested with the *Räumliches Rotieren* of the Leistungsprüfungssystem (LPS; Horn, 1983), where subjects had to rotate letters and numbers mentally (mean number of correct items during two minutes). All subjects were cursorily examined for their visual perception (e.g., superimposed figures, illusion contours, masked words; see a collocation Schnider, 1997) and praxia.

Persons with BIID received further neuropsychological testing. This comprised assessments of short-term memory and working memory for the verbal domain, using the Digit Span, as well as for the spatial domain, the Corsi Block Span (mean number of recalled sequences) (both this tests are from the revised Wechsler Memory Scale (WMS-R; Härtling et al., 2000). Verbal memory evaluated by the Verbal Learning Memory Test (VLMT; Helmstaedter et al., 2001) with a learning phase (mean of recalled words in five trials of a list of 15 words), a short-delay recall after presentation of an interference list and a 30-minutes delay recall (mean of words recalled) and a recognition assessment (mean of correctly recognized words minus false positive answers). Figural memory was tested by the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944) using the version Rey Complex Figure and Recognition Trial (RCFT; Meyers & Meyers, 1995) with a 3-minutes and a 30-minutes delayed recall (recalled mean elements, out of a possible score of 36) and recognition (mean of correctly recognized elements minus false positive answers out of a total score of 25). In addition, executive functions, such as phonemic fluency from the Regensburger Wortflüssigkeits-Test (RWT S-Words; Aschenbrenner et al., 2000) and nonverbal fluency (Five-Point-Test; Regard et al., 1982) using the version HAMASCH (Haid et al., 2002) were examined (number of correct words respectively figures minus errors in three minutes). For the examination of visual-constructional functioning the Osterrieth-Rey Complex Figure (version RCFT; Meyers & Meyers, 1995) had to be copied (total score out of 36).

Neuropsychological findings

In both groups normal neuropsychological functioning was revealed according to standardized norms (table 5 for the BIID group). No significant group differences were evident in any of the functional domains (table 6); particularly no reduced performance was shown in the four cognitive switching tasks (D-KEFS part 3 and 4, *Incompatibility*, *Flexibility*), as hypothesized. However, a significant correlation was found for the BIID group between the reaction times (RTs) of the *Incompatibility* task and the raw scores on the psychiatric rating scale (OCI) [rho = -0.645, p = 0.009]. Thus, the slower the RTs, the more pronounced were the obsessive-compulsive traits. No further correlations, or even trends, for the other three tasks, as well as for the control group were revealed (rho ≤ -0.237, p ≥ 0.395).

Table 5: BIID participants show normal cognitive functioning in extended neuropsychological examination

Measure	BIID participants (n=15)		
	Mean [hits]	SD	Mean of T-value [a]
Verbal Memory			
Short-term memory (Digit Span forward)	8.1	1.7	52.0
Working memory (Digit Span backward)	7.5	1.8	54.1
Learning (VLMT)	57.8	9.2	56.1
Recall after interference list (VLMT)	11.6	2.5	52.5
Recall after 30-minutes (VLMT)	11.6	2.1	52.0
Recognition (VLMT)	14.2	1.3	56.1
Nonverbal Memory			
Short-term memory (Corsi block forward)	8.7	1.6	52.2
Working memory (Corsi block backward)	9.1	1.6	55.4
Recall after 3-minutes (RCFT)	25.4	4.3	59.2
Recall after 30-minutes (RCFT)	23.6	4.6	57.4
Recognition (RCFT)	21.1	2.1	51.5
Executive Functions			
Phonemic fluency (RWT S)	20.6	7.8	46.1
Nonverbal fluency (HAMASCH)	36.7	8.8	52.7
Visual-construction (RCFT)	34.9	1.6	Group in the normal range

[a] Normal distribution from T-values ranging from 40 to 60 (M=50). T-values under 40 show a below-average cognitive performance, T-values above 60 an above-average cognitive performance.

Table 6: Neuropsychological examination revealed normal functioning and no significant differences between the group with BIID participants and control participants

Measure	BIID participants (n=15)		Control participants (n=15)		Statistics	
	Mean [sec]	**SD**	**Mean** [sec]	**SD**	**T-value (df = 28)**	**P-value**
Attention						
Speed, color naming (D-KEFS, part 1)	29.0	6.1	29.0	4.3	-0.17	0.87
Speed, reading (D-KEFS, part 2)	19.3	3.0	20.1	1.8	0.70	0.49
Selective attention (GoNogo, TAP)	533.0	65.3	527.7	68.4	0.22	0.83
Executive function						
Interference (D-KEFS, part 3)	51.1	14.4	50.5	8.4	-0.41	0.68
Flexibility (D-KEFS, part 4)	53.0	10.1	54.1	10.3	0.30	0.77
Incompatibility (TAP)	480.8	82.0	496.9	97.5	-.049	0.63
Flexibility (TAP)	741.6	273.8	775.3	277.6	-0.34	0.74
Mental spatial Orientation	[hits]		[hits]			
LEP	19.9	8.5	19.0	5.2	0.34	0.74

2.2.3 Neurology

Neurological status examinations revealed normal results in all persons with BIID (borderline in a 73-year-old), and in 14 of the control persons (one control person showed mild signs of a polyneuropathy and was excluded from the MRI analysis). Specifically no deficits could be found according to a sensory examination for pain, temperature, vibration and position sense.

2.2.4 Psychiatry

Method

In collaboration with a psychiatrist (PD Dr. med. Bernd Krämer) from the Psychiatric University Hospital of Zurich extensive psychiatric evaluation was realized to assess possible psychiatric co-morbidities from a broad range of disorders. The evaluation included the Structured Clinical Interview (SCID; Wittchen & Fydrich, 1997) for disorders according the Diagnostic and Statistical Manual of Mental Disorders (DSM) Disorders in a 2-hours-interview and required the completion of 14 self-rating questionnaires (listed below) covering psychological and psychiatric characteristics and symptoms (including, but not limited to symptoms of anxiety, depression, dissociation, autism, and schizotypal and obsessive-compulsive personality). Moreover, we evaluated sex-roles, body image, eating disorder and borderline disorder.
Self-rating questionnaires: Autismus-Spektrum-Quotient (AQ), Barratt Impulsiveness Scale (BIS 5), Borderline-Symptom-Liste (BSL), Bem Sex-Role-Inventory (BSRI), Depression Anxiety Stress Scale (DASS), Essstörung (EDI), Fragebogen zur Beurteilung des eigenen Körpers (FbeK), Fragebogen zu Dissoziativen Symptomen (FDS-20), Geschlechtsidentität (GI), Obsessive-Compulsive Inventory revised (OCI-R), Personal Attributes Questionnaire (PAQ), Sexuelle Präferenz (SP), Schizotypal Personality Questionnaire (SPQ-G), Körperdysmorphe Störung (YBOCS).

Psychiatric findings

BIID individuals and controls did not differ with respect to psychiatric disorders according to the SCID interview. Also, no differences were found regarding obsessive-compulsive, anxious, depressive and stress symptoms. However, we noted higher derealization and autoaggression scores, i.e., these symptoms are more common in the group of BIID individuals. They also showed a significantly higher body-dissatisfaction score. Additionally, we found a trend towards more borderline and conversion symptoms in BIID individuals. To sum up, from a psychiatric point of view we found a relatively unremarkable group of BIID individuals in comparison to controls. However, dissociation and conversion are promising candidates to contribute to the explanation of autoaggressive body-dissatisfaction in BIID individuals.

2.3 Behavioral Examination

2.3.1 Mental Limb Rotation

Introduction

If the picture of a hand is displayed in an unusual orientation and we have to decide whether it is a left or a right hand we normally rotate the picture mentally until we identify it as a left or a right hand. Such limb laterality decisions require a limbs mental rotation and involve networks that integrate spatial-visual and motor information of one’s body. These networks include superior parietal cortex, intraparietal sulcus, inferior parietal lobe and premotor cortex (Bonda et al., 1995; Kosslyn et al., 1998; Parsons, 1994; Shenton et al., 2004). The same brain areas were shown to be active during real movements, revealing a similarity between imagined and performed movements. Mental rotation tasks have a long tradition in behavioral neuroscience and have helped understand the multimodal anchoring of single limbs into a higher-order "body schema" (e.g., Parsons, 1987, 1994). In studies specific behavioral differences were found, such as right-handers respond faster to stimuli of a right than of a left hand (Gentilucci et al., 1998). Or backs of hands are faster recognized than palms, as long as fingers pointing up, medially or laterally (Parsons, 1987). And finally, left or right hands, whose fingers are pointing medially (i.e., toward the body’s centre) are faster classified than fingers that are pointing laterally (away from the body’s centre) (Parsons, 1994). Funk and Brugger (2008) termed this faster reaction pattern the "medial-over-lateral advantage" (MOLA). All these findings suggest that subjects implicitly ‘move’ an image of the own limb towards the screen and determine whether there is a match or a mismatch between visually presented and implicitly moved limb (Parsons et al., 1995). The more disparate a depicted limb is from the actual biomechanical body position the more time is required to mentally simulate it. Thus, mental rotation requires intact visuo-motor integration and a subject’s integration capability can be qualified by the response accuracy and time.
Do people respond differently to depicted limb stimuli if they have an altered anatomical body shape? Studies with people with a unilateral hand amelia (born without one hand) (Brugger et al., 2000; Funk & Brugger, 2008) or people with a unilateral upper limb amputation (Nico et al., 2004) showed slower reaction times (RTs) to hands corresponding to

their missing compared to their existing hand. Further, they showed longer RTs to hands in unnatural orientations (e.g., 180° rotation) than to those natural orientations (e.g., 0° presentation) as did normally limbed persons. In bilateral amelic participants, those with phantom sensations showed similar behavioral differences as the unilateral amelic participants, whereas those without phantom sensations did not show such a differentiation. Funk and Brugger (2008) suggest that phantom limbs in amelia may constrain mental rotation ability as much as amputation phantoms do.

Laterality decisions with feet have been recently examined with amputees with a unilateral amputation of the leg (Curtze et al., 2010). Participants had mentally to rotate feet in dorsal and plantar view in six different orientations. Despite the anatomical changes of the body, no difference to identify right and left feet stimuli was observed. What happens if people with BIID have to rotate a depicted foot that is not felt as integrated in the rest of their body (often described as '*unbeseelt*'). Even if they are physically able bodied people, do they show differences in rotation ability because of a possible less developed visuo-motor representation of the unwanted limb, similar to amputee without phantom sensations (Giummarra et al., 2011)? For persons with BIID we predict prolonged RTs in unnatural positions (e.g., that are difficult to reach with a real movement, as sole view or rotation angles of 180° and 270°) for the left feet that are arguably not properly represented. For the control group we also predict slower RTs for the left foot, however in this group due to its non-dominance (Curtze et al., 2010; Ionta et al., 2007). Further, for the hands we generally predict normal RTs for both groups, in accordance with the literature, demonstrating firstly that right-handers recognized right hands faster (Gentilucci et al., 1998), secondly, backs of hands are faster recognized than palms, as long as they do not point down (Parsons, 1987) and thirdly, hands with fingers pointing medially are faster classified than those pointing laterally (Parsons, 1994), shortly called MOLA-effect (Funk & Brugger, 2008). These last two predictions will also be examined for the feet in both groups.

Subjects

All participants of the study performed the task. However, to get a homogenous group concerning the handedness/footedness, as well as the side of amputation desire, we specifically analyzed the data of eight right-handed and right-footed subjects with a left-leg amputation desire (mean age = 46.9, SD = 14.6; see participants #1-8 in table 3, p. 19) and their matched control subjects (mean age = 48.1, SD = 11.5).

Design and Procedure

All participants responded to 128 randomized stimuli (4 repetitions of the 32 different stimuli), of which 64 were stimuli of hands (from Funk & Brugger, 2008) and 64 were stimuli of feet (photographs; see figure 3). Each limb (foot, hand) was shown of each laterality (left, right), in different views (dorsal/back, sole/palm) and at four different rotation angles (0°, 90°, 180° and 270°). Altogether, we had four independent variables (*limb, laterality, view, rotation angle*) and the dependent variables *correct RTs* and *accuracy*.

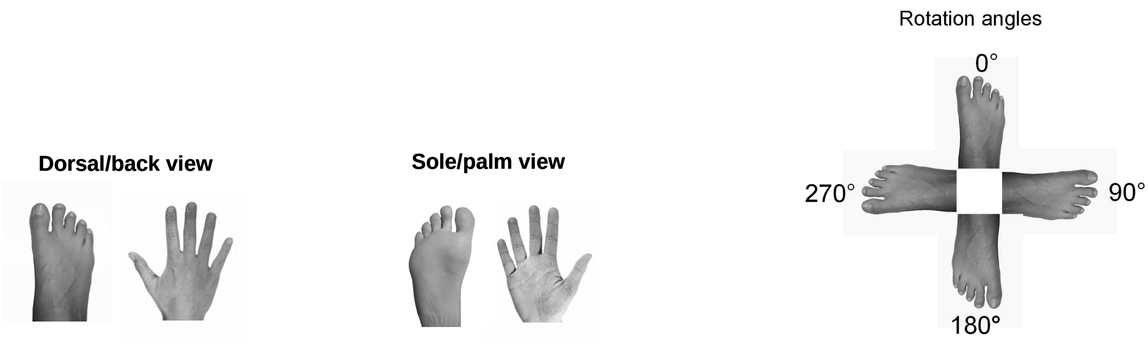


Figure 3: Stimuli. The right foot and hand presented in two views (dorsal/back, sole/palm) and four different rotation angles (0°, 90°, 108°, 270°). Left foot and hand stimuli were mirror images.

Subjects had their hands on the keyboard, covered by a cloth, and pressed for a depicted left foot or hand stimulus a left-sided key with their left index finger, respectively for a right foot or hand stimulus a right-sided key with their right index finger. Participants' feet were placed parallel and they were instructed not to move their feet during the task in order to prevent simplification of the task. Participants had to respond to the stimuli as quickly and as correctly as possible. A fixation cross was shown in the middle of the computer screen during 1 second between each stimulus. Subjects terminated the stimulus exposure by pressing the specific key. The sequence of stimuli was randomized for each participant. Stimulus presentation and response collection were controlled by E-prime software Version 2.0 (Psychology Software Tools).

All participants scored in the normal range in a standardized paper-pencil test for mental letter and number rotation (LPS; Horn, 1983), as well as in cursory examined paper-pencil tasks for hands and feet. So, results should not be influenced by general deficits in mental imagery.

Data analysis

RTs for correct responded trials were analyzed. Firstly, RTs equal or more than 7000 milliseconds (ms) were deleted (2.3%). Secondly, individual means for each stimulus category (e.g., left hand, back view, 90° rotation angle) more than 2 SDs away from the groups mean RT were replaced (3.3%) by the specific group RT plus two SDs. A training session of 12 trials (two third of the trials had to be correct to continue the task) was discarded from the analysis. The analysis was performed using SPSS 18 statistical software and Stat View 5.0.1. The data was analyzed using the repeated measures analysis of variance (ANOVA) test. To evaluate a possible effect of the unwanted left leg, the dependent variables – correct RT and accuracy –, were calculated in two separate three-way ANOVAs for *laterality* (unwanted, accepted), *view* (dorsal/back, sole/palm) and *rotation angle* (0°, 90°, 180°, 270°) as within-subjects factors, separately for feet and for hand stimuli and separately for persons with BIID and control persons. Further, to compare people with BIID and controls two four-way ANOVAs were computed, with group (BIID/controls) as between-subject factor, again separately for feet and hands. Moreover, t-Tests were done to assess group differences concerning the MOLA with the factors laterality, view and rotation angle for feet and hands.

Results

Foot stimuli for each group (three-way ANOVA)

For each group significant main effects and interactions for foot and hand stimuli are listed in table 7. In the BIID group the correct RTs for feet stimuli revealed no main effect for *laterality* [$F(1, 7) = 1.31$, $p > 0.29$], nor interactions with the left unwanted foot, as *laterality x view* [$F(1, 7) = .86$, $p = 0.385$] or *laterality x rotation angle* [$F(3, 21) = 2.94$, $p = .103$], indicating that against our hypothesis, no prolonged RTs to stimuli of the unwanted left were revealed. Also in the control group no main effect for *laterality* [$F(1, 7) = .574$, $p = 0.474$], as well as no interactions with *laterality* were found [*laterality x view:* $F(1, 7) = .1.6$, $p = 0.247$;

laterality x rotation angle: F(3, 21) = 0.491, p = 0.692], indicating that no slower RTs of the non-dominant left foot was detected, as hypothesized. The main effect *rotation* angle was only significant in the control group, indicating increased RTs for the 180° rotation angle.

Firstly, as described above, no faster RTs can be found for the dominant right foot, neither in the control group, nor in the BIID group. Second, for both groups feet in dorsal view were faster identified than those from sole view, as long as the toes point up or to the sides (0°, 90° and 270°). For dorsal views pointing down (180°) no such advantage is revealed. Thirdly, a MOLA for RTs reached significant level in the BIID group for both feet [Left: (t(7) = -2.996, p = .01, one-sided); Right: (t(7) = -2.116, p = 0.036, one-sided], indicating that medially pointing toes (to the centre of the body) were faster classified than laterally pointing toes. However, in the control group only a tendency for a MOLA for the left foot was found [(t(7) = -1.622, p = .074, one-sided)], but none for the right foot [(t(7) = 0.980, p = .490, one-sided]. Analysis of the accuracy revealed for both groups only the significant main factor *view* [BIID group: F(1, 7) = 5.83, p = 0.035], [Control group: F(1, 7) = 10.72, p = 0.014], pointing to more precise identification of stimuli in dorsal/back view.

Hand stimuli for each group (three-way ANOVA)

In table 1 the significant effects of hand stimuli, separately for each group are listed. First, in the BIID group we found a faster performance to identify the dominant right hands. Interestingly, no significantly faster RTs to the dominant right hand were yielded in the control group [F(1, 7) = .574, p = 0.474]. Second, in accordance with the feet stimuli, for both groups, hands in back view were faster identified than those in palm view, as long as the fingers point up or to the sides (0°, 90° and 270°). For back views of hands pointing down (180°) no such advantage is given. And thirdly, there was only a tendency of a MOLA in the BIID group for the left hand [(t(7) = -1.504, p = .088, one-sided], but not for the right hand [(t(7) = -0.949, p = .374, one-sided)]. In the control group a scarcely significant MOLA effect was revealed for the left hand [(t(7) = -1.912, p = .049, one-sided], but only tendential for the right hand [(t(7) = -1.68, p = .069, one-sided].

Accuracy of hand stimuli did not reveal any significant level in the main factors or interactions in both groups, however two tendencies were observed for the control group [rotation angle: F(3, 21) = 3.080, p = .054; laterality x rotation angle: F(3, 21) = 3.011, p = .053], pointing to less accurate responses for rotation angles at 180°, especially for the left hand.

Table 7: Mean reaction times (RTs) for feet and hands, separately for each group. Significant main effects and interactions for the foot and hand stimuli (three-way ANOVA) and descriptions

Group [each n=8]	Significant main effects and interactions	*F* value/*p* value	Description
Feet			
BIID	View	$F(1,7) = 14.55$, $p = .007$	Dorsal of feet faster than soles
BIID	View x Rotation angle	$F(3,21) = 8.70$, $p = .001$	Dorsal of feet faster in 0°, 90° and 270°; see figure 2
Control	View	$F(1,7) = 34.96$, $p = .001$	Dorsal of feet faster than soles
Control	Rotation angle	$F(3,21) = 13.13$, $p = .000$	Increased RTs for rotation angle 180°
Control	View x Rotation angle	$F(3,21) = 8.62$, $p = .001$	Dorsal of feet faster in 0°, 90° and 270°; see figure 2
Hands			
BIID	Laterality	$F(1,7) = 12.05$, $p = .010$	Right hands faster than left hands
BIID	Rotation angle	$F(3,21) = 22.89$, $p = .000$	Increased RTs for rotation angle 180°
Control	View	$F(1,7) = 14.56$, $p = .007$	Backs of hands faster than palms
Control	Rotation angle	$F(3,21) = 26.24$, $p = .000$	Increased RTs for rotation angle 180°
Control	View x Rotation angle	$F(3,21) = 4.82$, $p = .010$	Back of hands faster in 0°, 90° and 270°

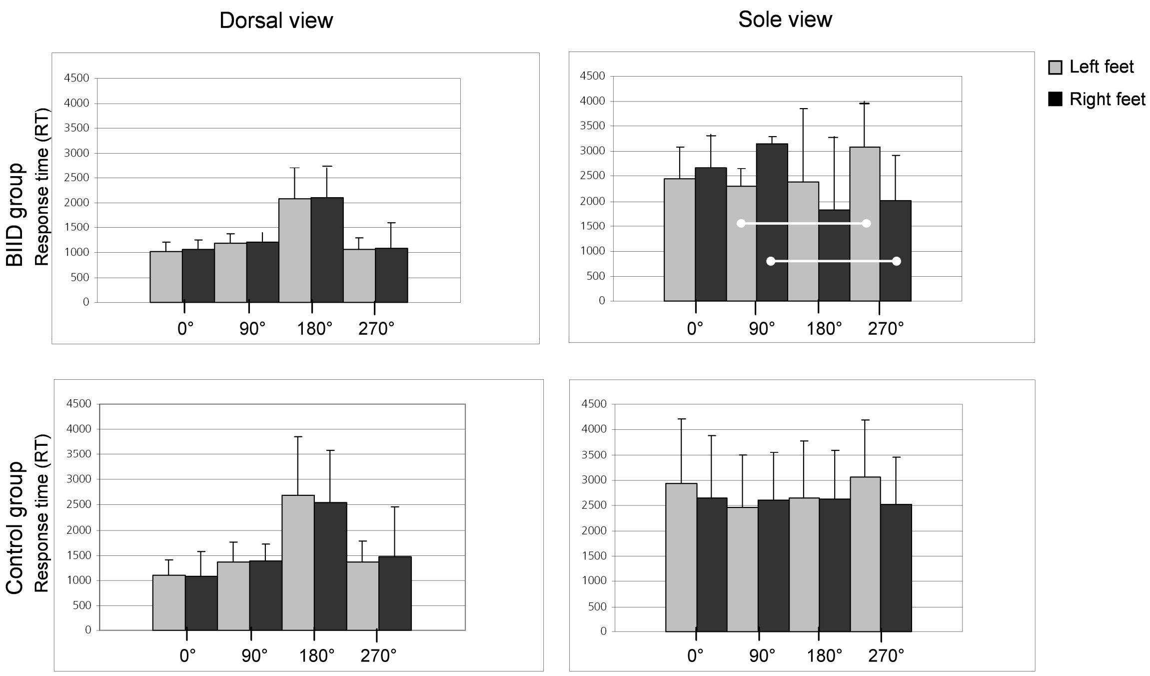


Figure 4: Mean reaction times (RTs) for feet. Mean RTs by group (BIID group, n=8; Control group n=8) for different views (dorsal, sole) and laterality (left/unwanted and right/accepted). In the upper right panel the two white lines show an example of a "medial-over-lateral-advantage" (MOLA) for the left (bright grey) and right feet (dark grey) i.e., faster responses for the medial than for the lateral feet. Error bars depict the standard error of the mean.

Feet and hand stimuli compared by groups (four-way ANOVA)

Contrasting the group of BIID with the control group for feet in two four-way ANOVAs, for correct RTs and accuracy, yielded significant main effects and interactions that are shown in table 8. The between-subject factor *group* was not significant [RT: F(1, 14) = 0.43, p = 5.25; Accuracy: F(1, 14) = 0.11, p = 0.74]. No significant effect was found for the main effect *laterality* [F(1, 14) = 1.33, p = 0.27] and the interaction *laterality x group* [F(1, 14) = 0.054, p = 0.819]. A tendency was found for the interaction *rotation angle x group* [F(3, 42) = 2.56, p = 0.068], indicating that subjects with BIID performed faster RTs for all rotation angles – except almost equal RTs in the rotation angle at 90° – compared to controls. Another tendency was shown for the interaction *laterality x rotation angle* [F(3, 42) = 2.96, p = 0.054], whereas left feet were faster identified at 0° and 90° and right feet faster at 180° and 270° rotation angles. Both these tendencies were significant for the hand trials in the four-way ANOVA, also depicted in table 2, indicating the same nature.

In a five-way ANOVA the additional within-factor *limb* (foot, hand) did not reach significant level [F(1, 14) = 0.086, p = 0.774].

Table 8: Mean reaction times for feet and hands for both groups. Significant main effects and interactions for the two four-way ANOVAs (one for feet and one for hands) with group as between-subject factor

Group [n=16]	Significant main effects and interactions	*F* value/*p* value	Description
Feet			
	View	*F*(1,14) = 40.04, p = .000	Dorsal of feet faster than soles
	Rotation angle	*F*(3,42) = 9.55, p = .000	Increased RTs for rotation angle 180°
	View x Rotation angle	*F*(3,42) = 16.88, p = .000	Dorsal of feet faster in 0°, 90° and 270°
Hands			
	View	*F*(1,14) = 13.07, p = .003	Back of hands faster than palms
	Rotation angle	*F*(3,42) = 47.00, p = .000	Increased RTs for rotation angle 180°
	Rotation angle x group	*F*(3,42) = 3.54, p = .041	Faster RTs of BIID group in 90°, 180° and 270°
	Laterality x rotation angle	*F*(3,42) = 4.13, p = .019	Right hand faster in 180° and 270°
	View x rotation angle	*F*(3,42) = 6.51, p = .005	Back of hands faster in 0°, 90° and 270°

Discussion

The ability to perform mental rotation of limbs can be altered by peripheral changes of the body shape, as in amputees missing an arm (Nico et al., 2004), or in patients with changed peripheral function of the body by preserved body shape as in focal hand dystonia (Fiorio et al., 2006) or chronic arm pain (Schwoebel et al., 2001). In these patients slower RTs were observed in mentally rotating pictures of the affected right dominant hand related to the degree of unnatural positions (the more difficult to mentally reach the depicted hand the longer the responses for the affected hand). Fiorio et al. (2006) additionally examined mental rotation of the unaffected feet of their patients with focal hand dystonia and could not find such an effect.

The present study explored whether people with BIID, having a preserved body shape and no known peripheral neurological abnormalities, differ in mentally rotating their unwanted versus their accepted leg. We predict that our sample of right-handed and -footed people with BIID show prolonged RTs to stimuli of the left unwanted foot compared to the right accepted foot. This assumed difficulty to mentally rotate and classify the undesired limb as right or left limb, bases on a not properly representation of the leg that may constrain mental imagery of the specific limb. The cause of BIID is not known, however we assume cerebral differences of the representation of the unwanted limb that could be due to a decreased integration of multisensory information, including visuo-motor information.

Feet

In a task subjects had to mentally rotate feet and hands in four different rotation angles (0°, 90°, 180°, 270°). Our first hypothesis must be rejected, as mental limb laterality decisions did not reveal prolonged correct RTs for the left foot (unwanted foot for subjects with BIID, respectively non-dominant foot for control subjects) and its interactions with view and rotation angles (unnatural positions). Also Curtze et al. (2010), examining mental rotation with unilateral leg amputees, detected no significant main effect for laterality, nor interactions for this experimental group, but found a significant main effect for laterality in the control group. The authors suggest that the amputees may have judged on a more abstract knowledge than referring to a representation of the own one-legged body. Although, the results of the amputees show typically strong effects of view and orientation angle (e.g., slower performance for more biomechanically difficult orientations and views) suggesting at least a partial use of motor strategy to rotate ones' limb mentally to the position of the depicted stimulus. The same explanation could be obtained for our sample, as about one third of all participants performed the task strategically on abstract decisions, when they were asked after having finished the task. A laterality task on a higher demanding level could probably reduce the use of abstract knowledge.

Although, we could not show a laterality effect, our data reveals the mentioned typically strong effects of view and rotation angle found in studies (Curtze et al., 2010; Ionta et al., 2007), suggesting that subjects implicitly ‘moved’ an image of the own limb towards the screen and determined whether there was a match or a mismatch between visually presented and implicitly moved limb (Parsons et al., 1995). According to literature both groups identified dorsal views faster and more accurate than sole views, as long as the toes point up or to the sides (0°, 90° and 270°) (Parsons, 1987). Interestingly, a "medial-over-lateral-advantage" (MOLA) could only be found for the BIID group, for both feet, whereas the control group showed only a tendency for a MOLA for the left, but no effect for the right foot. In literature no studies examining a MOLA effect in feet were found. Regarding figure 4 both groups revealed no MOLA for both feet in dorsal view, however the group with BIID shows faster RTs to medially pointing feet (left foot at 90° and right foot at 270°), than to laterally pointing feet (right foot at 90° and left foot at 270°). In the control group only smaller effects can be observed (especially faster RTs for left foot at 90°, than for left foot at 270°). This leads to the assumption that a MOLA for feet could also exist for sole view, as biomechanically a ‘lateral’ pointing feet, is more difficult to perform and therefore more time consuming to imagine compared to a ‘medial’ pointing feet. However, why people with BIID show this MOLA effect additionally for the right foot can only be speculated.

Contrasting both groups in one ANOVA, two tendencies were shown, whereupon subjects with BIID showed tendentially faster RTs for all rotation angles (group x rotation angle), especially at 180° and the second tendency showed faster RTs for both groups identifying left feet at 0° and 90°, whereas right feet were faster identified at a 180° and 270° rotation angle (laterality x rotation angle).

Hands

Faster proceeding of right hands was found for the group with BIID, but surprisingly not for the control group (even no tendency). Whereas subjects with BIID responded faster to right hand stimuli at all rotation angles, controls detected right hands faster in more unnatural orientations (at 180° and 270°) and left hands faster in natural orientations (at 0° and 90°). In accordance to literature (e.g., Parsons, 1987) both groups identified back views faster and more accurate than sole views, as long as the fingers point up or to the sides (0°, 90° and 270°), whereas for stimuli in palm views at 180° the slowest RTs were revealed. The control group showed a significant MOLA effect for the left hand, whereas the BIID group only presented a tendency. For the right hand a MOLA effect is tendentially presented in the control group, whilst no MOLA is shown in the BIID group. In contrast to the feet stimuli, where a MOLA was only detected for the sole views, we found for the hand stimuli MOLA effects for both views, larger pronounced for the control group in classifying the left hands. The detected MOLA tendencies in the BIID are caused by different interactions, except for right hands in sole view.

Contrasting both groups with hand stimuli, subjects with BIID showed faster RTs for all rotation angles (group x rotation angle) than controls, especially at 180°. And further, left feet were faster identified at 90°, whereas right feet were faster identified at a 180° and 270° rotation angle (laterality x rotation angle). Almost equally fast were both hands classified at a rotation angle of 0°.

Summing up, firstly, in the group with BIID mental rotation did not lead to prolonged RTs for the unwanted, hypothetically less cerebrally represented left leg, despite of different levels of trial difficulty used. However, also the control group did not differ in RTs to the left or right foot, what would be expected due to faster RTs to the dominant foot shown in the literature. Presumably, subjects decided on the basis of a more abstract knowledge than directly referring to the representation of their own body. Mental rotation tasks that diminish such decisions on an abstract knowledge (e.g., more complex biomechanical postures) could be more qualified to detect differences for limbs that are not felt to be integrated. Secondly, in our task no other relevant anomalies could be detected for the group with BIID or the control group. For example, response patterns typically observed in mental rotation tasks emerged in both groups for both feet and hands. For instance, there was a faster identification of dorsal than back views, when presented at 0°, 90° and 270° (Parsons, 1987). With respect to the MOLA, less pronounced results were obtained, as a MOLA for both feet was only showed for the group with BIID, whereas in the control group only a tendency for the left foot was detected. In contrast, MOLA for hand stimuli were found in the control for left hand stimuli and tendentially in the BIID.

2.3.2 Body Transformation and Task Switching

Introduction

Imagining the own body and mentally transform it into a specific view (e.g., into a front facing position) has been investigated in healthy people and patients. These tasks are labeled ”mental own body transformation” (e.g., Arzy et al., 2006; Arzy et al., 2007; Blanke et al., 2005; Mohr et al., 2006). In addition to the mental rotation of the undesired foot in BIID, reported in the preceding chapter (2.3.1), we aimed to examine in the present study, how people with BIID mentally transform a body that is either depicted with their desired leg amputation (here, left leg) compared to a not desired leg amputation (right leg). Any perspective transformation (mental own body transformation) is thought to reflect visuo-motor integration of one’s entire body. Specifically, the two different mental body tasks used in our paradigm (modified after Easton, et al., 2009) are known to activate the temporal parietal junction (TPJ) and the lateral temporo-occipital cortex (Arzy et al., 2006). In one task participants see a human figure on the screen and have to mentally take its position (out of body transformation task, here OBT task). In the other task, participants have to imagine that the figure is their own reflection in a mirror (embodied self-location, here Mirror task; Arzy et al., 2006). Easton et al. (2009) suggest that both tasks involve the body schema in activating mainly visual and spatial information, but that they differ in the perspective processing. Thus, in the OBT-task participants have to mentally transform themselves into the depicted human figure (to take a rather disembodied perspective), whereas in the Mirror task, they are instructed to observe their own reflection (to keep a clearly embodied perspective). We hypothesized, first for the group with BIID, a faster perspective transformation and therefore faster reaction times for those displays, which correspond to the desired amputation (here left-leg amputated body) for both tasks, due to a faster visual-motor integration.

In addition to the first attempt to quantify bodily components, we further investigated a possible non-bodily (psychiatric) component of BIID. The two tasks (OBT and Mirror) were presented in a haphazard order with a specified ratio of frequent and rare presentations (see *Design* and *Procedure*), so that people had to switch between OBT and Mirror stimuli. The costs by switching between the two tasks were assessed. They are thought to be an indicator of fronto-parietal connectivity (see overview in Easton et al., 2009). With respect to BIID, the ability of cognitive switching may be reduced in some individuals. This link rests on a discussion in associating BIID with obsessive compulsive characteristics, e.g., individuals with BIID often report a repetitive imagination of being in the desired body shape or an urge to pretend to be amputated (Braam et al., 2006; Thiel et al., 2009). As patients with obsessive compulsive disorder seem to be primarily impaired in switching tasks (thought to be processed mainly by the lateral OFC (Chamberlain et al., 2008), BIID could also entail a tendency of reduced switching performance. Against this background, our second hypothesis was the prediction that there were enhanced switch times between the two tasks in participants with BIID, especially for those participants with enhanced obsessive compulsive traits, as revealed in our psychiatric examination (see chapter 2.2.4).

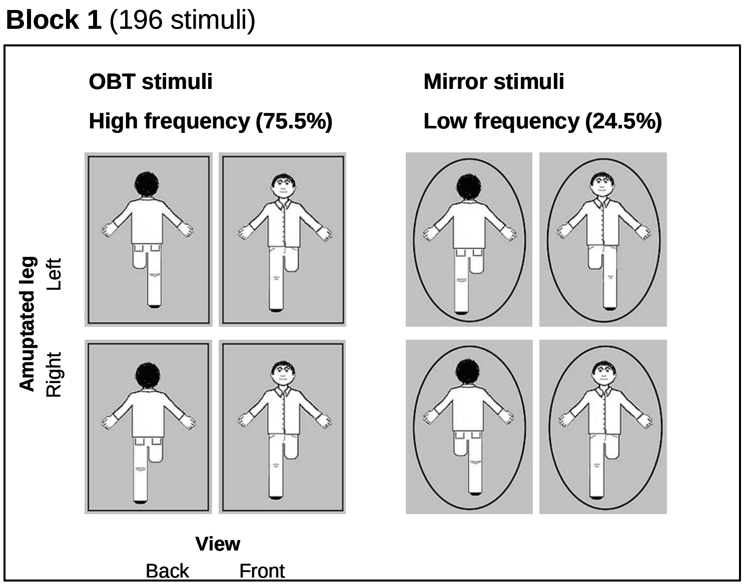
Subjects

All participants performed this task. However, as in the Mental Rotation task (chapter 2.3.1) we chose a homogenous group of seven people with BIID, including right-handed and right-footed subjects with a left-sided leg amputation desire (mean age = 44.0 years, SD = 13 years; see participants #1-7 in table 3, p. 19), not older than 60 years (due to an age-related increase in reaction times) and their matched control subjects (mean age = 46.0 years, SD = 10 years).

Design and Procedure

We modified the method introduced in Easton et al. (2009). Participants sat in front a screen and had to respond to 8 different leg-amputated human figures, repeatedly presented in a pseudo-randomized sequence. There were two different mental own body imagery tasks (OBT and Mirror) to assess the switch costs between them: In one task the human figure was shown in a rectangular box and subjects had to mentally imagine being in the position of this depicted human figure (OBT task; disembodied self-location mimicking an amputated person). In the second task, the human figure was shown in an oval shape and the subject had to imagine that the figure is their own reflection in a mirror (Mirror-task; embodied self-location; figure 5). In both tasks participants had to judge, if a left or right leg amputation was presented. Furthermore, the human figures were either shown in back view (back-facing) or in frontal view (front-facing). For a left leg amputation the subjects were instructed to press a left-sided key with their left index finger, for a right leg amputation a right-sided key with their right index finger. Participants had to respond as quickly and as correctly as possible (see stimulus presentation and software chapter 2.3.1). In an additionally assessed paper-pencil task for mental rotation (Horn, 1983) all participants scored in the normal range.

A



B

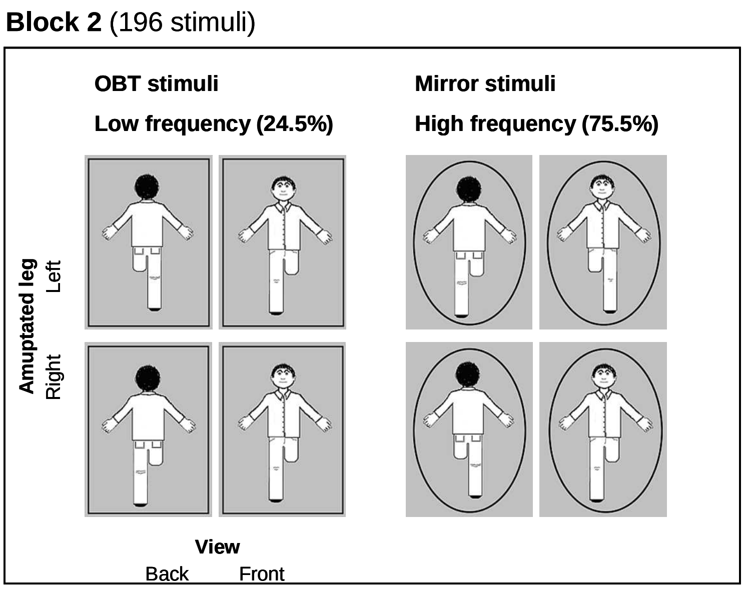


Figure 5: Stimuli and Design. In A (block 1) and B (block 2) the eight different human figures are shown, separated into task (OBT and Mirror) and alternative frequency (high, low). Each human figure has an amputated leg (left, right) and is shown in two views (back, front). The rectangular box indicated that participants had mentally to take the position of the human figure (OBT task) and the oval form indicated that they had to imagine seeing their own reflection (Mirror task).

The participants responded to a total of 392 trials, which presented the 8 different stimuli (4 OBT and 4 Mirror stimuli) randomly. There were two blocks of 196 stimuli each, with a short break in between. Within each block, the two stimulus types were presented in a different ratio, such as in the first block 75.5% OBT stimuli (148 stimuli with 37 repetitions of each of the 4 stimuli) and 24.5% Mirror stimuli (48 stimuli with 12 repetitions of the 4 stimuli) were presented. In block two the ratio of the OBT and Mirror stimuli was reversed, so that both stimulus types were presented in one block frequently (*high* frequency) and in the other rarely (*low* frequency, i.e., involving more switching performance). In half of the participants the order of block presentation was interchanged, beginning either with block 1 (more OBT stimuli) or block 2 (more Mirror stimuli). A practice block of 20 trials preceded the experiment proper (data not further analyzed). The experimental blocks took about 13 minutes.

Altogether, we had four independent variables, first the *frequency* of trial (high, low), the *task* (OBT, Mirror), *amputation* (left leg, right leg) and *view* (back, front).

Data analysis

RTs for correct trials were analyzed. According to previous studies (Easton et al., 2009; Kiesel et al., 2007; Miyake et al., 2000), RTs smaller or larger than 3 SDs the participants' mean in each category (e.g., Mirror stimuli in block 1 of the right leg in frontal view) were removed. The analysis was performed using SPSS 18 statistical software and Stat View 5.0.1. Repeated measures analysis of variance (ANOVAs) were calculated. To evaluate a possible effect of the unwanted left leg, the dependent variables – correct RT and accuracy –, were calculated in two five-way ANOVAs for *frequency* (high, low), *task* (Mirror task, OBT task), *amputation* (left/unwanted, right/accepted) and *view* (back, front) as within-subjects factors to compare the group with BIID and control group. Further, we performed correct RT and accuracy separately for persons with BIID and control persons with two three-way ANOVAs for the same within-factors (frequency, task, amputation and view). To assess a possible relation between switching times and obsessive compulsive traits (OCI questionnaire, from psychiatric examination), the mean RT of the switching trials were correlated with the total OCI score for each group.

Results

The significant group main effects and interactions are listed in table 9, those separately analyzed for both groups are listed in table 10.

Contrasting the group of BIID with the control group in two five-way ANOVAs, for correct RTs and accuracy, did not yield a significant between-subject factor *group* [RT: F(1, 12) = 0.99, p = 0.759; Accuracy: F(1, 12) = 0.49, p = 0.496]. Calculating the correct RTs for our predicted interaction *amputation x group*, revealed only a tendency [F(1, 12) = 3.678, p = 0.079], indicating for the group with BIID tendentially faster RTs for left-leg amputated human figures than for right-sided amputations and reversed for the control group (figure 6A). No other interactions with *amputation* were shown to be significant between groups. There was a main effect of *frequency* [F(1, 12) = 6.46, p = 0.026], indicating that both groups had longer RTs in the low-frequency than in the high-frequency condition (figure 6B). Moreover, the main effect *task* was significant as well [F(1, 12) = 12.46, p = 0.004] (description see below in *task x group*). The main factor *view* tendentially differed [F(1, 12) = 12.46, p = 0.078], in showing prolonged RTs for human figures in back view and faster RTs in frontal view. Regarding the significant interactions, *task x group* yielded to be significant [F(1, 12) = 10.81, p = 0.006], indicating that the BIID group responded faster to OBT stimuli, than to Mirror stimuli, whereas the control group did not differ between them (figure 6C). Another significant interaction was found in *task x view* [F(1, 12) = 10.55, p = 0.007], showing faster RTs to Mirror stimuli in frontal view (known to be easier), than in back view (known to be more difficult) and almost equally RTs to frontal and back view stimuli in OBT task.

For the second dependent variable – accuracy – no main effects or interactions were significant.

Table 9: Mean reaction times (RTs) for body transformation and switching for both groups: Significant main effects and interactions for the five-way ANOVA with group as between-subject factor and description.

Group [n=14]	Significant main effects and interactions	*F* value/*p* value	Description
	Frequency	*F*(1,12) = 6.46, p = .026	High frequent stimuli faster than low frequent stimuli
	Task	*F*(1,12) = 12.46, p = .004	OBT stimuli faster than Mirror stimuli
	Task x group	*F*(1,12) = 10.81, p = .006	OBT stimuli faster than Mirror stimuli in the BIID group
	Task x view	*F*(1,12) = 10.55, p = .007	Mirror stimuli in frontal view faster than in back view

Analogous analyses performed analyses performed for the two participant groups separately (see table 10) revealed for individuals with BIID for the RTs of correct responses only a slight tendency for *amputation* [F(1, 6) = 3.43, p = 0.113], indicating, corresponding to our hypothesis, numerically faster RTs to left-leg amputated than to right-leg amputated human figures (figure 6A). No significant interactions with the factor *amputation* were found. The control group did not show a corresponding main effect (nor even a trend) for the factor *amputation* [F(1, 6) = 1.27, p = 0.302] nor any interaction [F-values ≤ 2.98; corresponding p-values ≥ 0.135]. The main effect *frequency* was only significant in the control group [F(1, 6) = 12.41, p = 0.012], indicating faster RTs to high, than to low frequent stimuli. In contrast, the group with BIID, did not show significant switch costs [F(1, 6) = 0.95, p = 0.367] (figure 6B). Furthermore, the main effect *task* was only significant for the BIID group [F(1, 6) = 13.664, p = 0.010] and not for the control group, pointing to faster RTs to OBT stimuli, compared to Mirror stimuli (figure 6C). Finally, the interaction *task x view* fell short from significance in the control group [F(1, 6) = 5.85, p = 0.052] and yielded only a tendency in the BIID group [F(1, 6) = 4.75, p = 0.072], indicating faster RTs to Mirror stimuli in front view, compared to back view for both groups. Also OBT stimuli were faster responded to back than in front view in the control group, whereas the BIID group did not show a difference for the two views.

Analyses of the accuracy data did not reveal any significant main effect or interactions (in neither group).

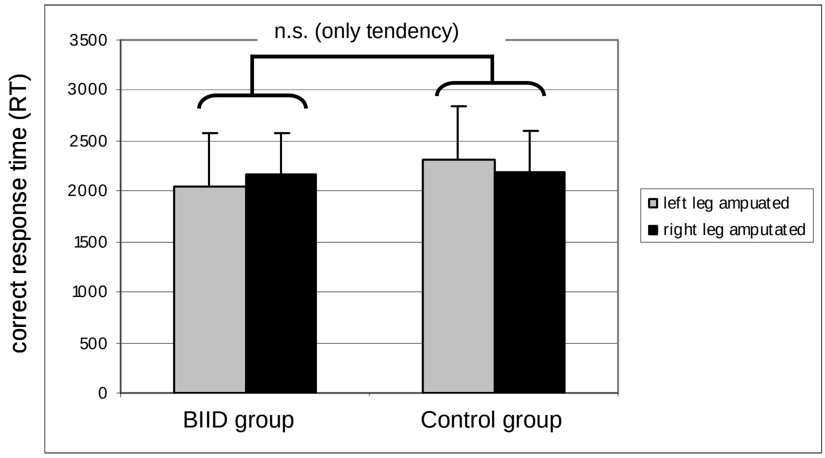
Correlation between individual OCI scores and mean RTs to switch trials revealed no significant relation for neither group (BIID group: rho = 0.667, p = 0.102; Control group: rho = 0.848, p = 0.939) (Note that if Pearson correlation instead of Spearman are calculated, the respective values are: BIID group: r = 0.613, p = 0.144; Control group: r = 0.511, p = 0.242).

Table 10: Mean reaction times (RTs) separately for each group: Significant main effect and interaction (four-way ANOVA) and a description of the direction of the observed effect.

Group [each n=7]	Significant main effects and interactions	*F* value/*p* value	Description
BIID	Task	*F*(1,6) = 13.664, p = .010	OBT stimuli faster than Mirror stimuli
Control	Frequency	*F*(1,6) = 12.41, p = .012	High frequent stimuli faster than low frequent stimuli (switch costs)

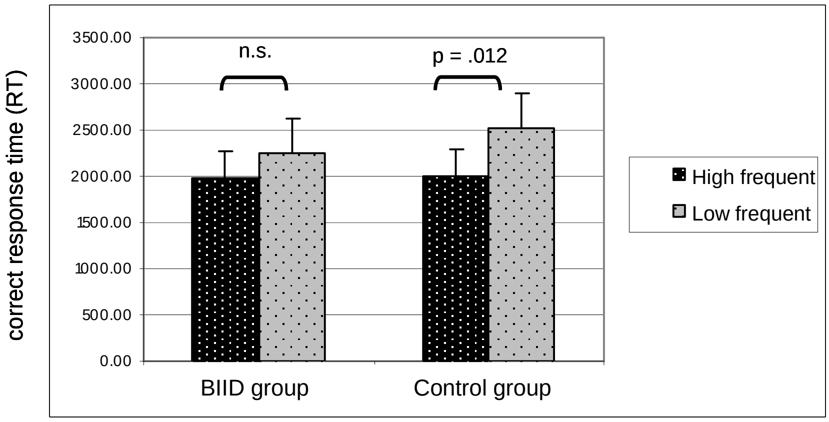
A

Interaction amputation x group



B

Main effect frequency (high, low)



C

Interaction task x group

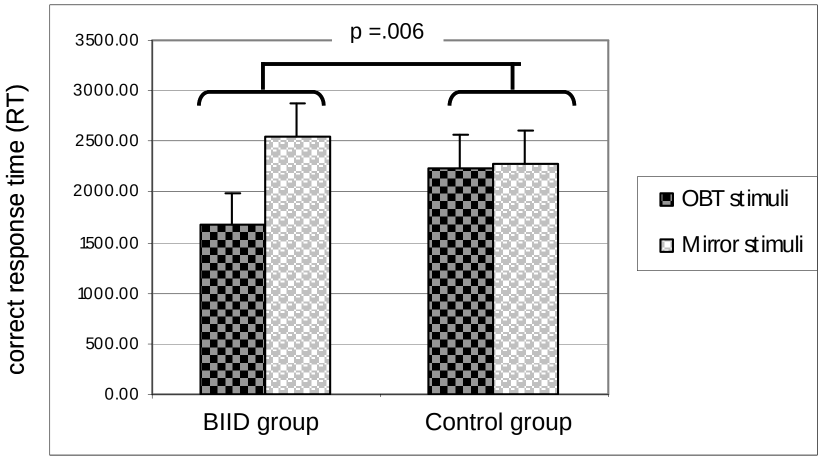


Figure 6, A-C (p. 44) Mean correct RTs displayed for the two groups (BIID, control).
A) Depicted is a trend (n.s., p = .079) for our first hypothesis according to RTs for left-leg (grey color) and right-leg (black color) amputated human figures. The group with BIID, but not the control group, showed numerically faster RTs to the left-leg amputation stimuli (desired), than for right-leg amputation stimuli (n.s., p = 0.113). Error bars are standard errors of the mean. **B)** Displayed are switch costs (second hypothesis), when alternating between the high frequently and low frequently presented stimuli. In opposition to our predicted in our second hypothesis, in the BIID group no significantly enhanced switch costs were found, but such an effect showed up in the control group. **C)** Shown are the RTs to OBT stimuli (disembodied task in rectangular shape figure 5) versus Mirror stimuli (embodied task in oval shape in figure 5). The group with BIID, but not the control group, showed faster RTs for OBT than Mirror stimuli.

Discussion

In the present study we investigated how people with BIID mentally transform a body that is either depicted in a desire-compatible or desire-in-compatible body shape to infer about the underlying body-related multisensory information processing. We were specifically interested if people with BIID would show faster mental transformations of specifically the amputated human figure that matches their desired body shape. For this first prediction, we only found a tendency in the group of BIID in faster RTs (i.e., faster perspective transformation) to human figures presented with a left leg amputation (figure 6A). In contrast, the control group showed slightly faster RTs (but not even a statistical trend) to right-leg amputations. However, in the analysis within the BIID group no RT advantage for desired compared to non desired leg amputations was found. The trend in the group comparison is in line with our hypothesis of faster visuo-motor integration in people with BIID in mentally transforming the perspective of a desired body shape with a left leg amputation. An underlying altered neural mechanism (probably observed by the temporo-parietal area) and connected areas could have facilitated the mental imagery required for this task. Possible early ontogenetic alterations or a lifelong imagination or experiences of pretending to be in the desired body shape could be conceivable for this observed trend. Some support emerges from our questionnaire data (Zurich BIID Scale; chapter 2.1.2). Showing that pretending behavior was rated to be important in the here presented subgroup of BIID individuals (Mean score of assessing pretending behavior = 4.2; from a scale from 1 "strongly disagree [not important at all]" to 6 "strongly agree [very important]"). However, the predicted trends did not reach the significance level to verify our hypothesis of faster visuo-motor integration of the desired body shape.

Our second prediction has to be clearly rejected, as no enhanced switching costs were shown in people with BIID. This was assumed on the basis of a possible link to obsessive compulsive characteristics that are normally accompanied by such a reduced cognitive switching performance (Chamberlain et al., 2005, 2008; Head et al., 1989). In contrast, the control group had significant switch costs in alternating between low and high frequently presented trials (figure 6B). On the basis of our psychiatric examination, the link between our BIID sample and obsessive compulsive characteristics is no longer justified, as our participants with BIID scored in the normal range in questions assessing OCD (OCI, Foa et al., 2002). Also, our sample performed as accurately as the control group in tasks assessing verbal and nonverbal flexibility and switching. Why the control group showed significant switch costs in the present task, but not in the general neuropsychological examination may be explained by the specific mental transformations of the former task.

Beside the test of our two hypotheses, we made some observations pertaining to previous studies requiring mental own-body-imagery. For instance, participants in both groups were faster for human figures in front view compared to back view applied for Mirror stimuli (Arzy et al., 2006; Easton et al., 2009). Further, and not congruent with the literature, in the OBT task we did only find a slight trend in the control group for superiority of speed to human figures in back view than in front view (Arzy et al., 2006; Arzy et al., 2007; Blanke et al., 2005; Easton et al., 2009; Mohr et al., 2006; Zacks et al., 1999). The group with BIID showed comparable RTs to both views. RT advantage to back views in OBT task could have been expected, because it is easier to respond to body positions that match to the actual body position, when sitting in front of the screen. Moreover, in both groups we found (in accordance with the literature) faster performance for the OBT stimuli than for the Mirror stimuli (figure 6C), an effect that was especially pronounced in the BIID group (Arzy et al., 2006; Easton et al., 2009). Easton et al. (2009) explained this effect by pointing out that mental imagery of a disembodied self-location and perspective (OBT task) should be easier to perform than mental imagery requiring an embodied self-location and perspective (Mirror task). They assumed that the first and easier process might be based on an extrinsic egocentric coordinate system and the second and more difficult process to an intrinsic egocentric coordinate system.

In general, tasks of mental own body imagery were administrated to individuals along the schizophrenia spectrum and people with transient out-of-body experiences (Arzy et al., 2007;

Blanke et al., 2005; Easton et al., 2009; Mohr et al., 2005). The authors suggest that this kind of tasks seems to be valuable in the investigation of a disturbed self representation, such as loss of agency or delusions of alien control in schizophrenic patients or in the transient disembodiment and altered visuo-spatial perspective assumed to be at the heart of out-of-body experiences. They propose that an intact bodily self representation requires a normal integration of multisensory information (e.g., vision, motor or spatial references) by temporo-parietal regions. Consequently, the information would generate an intact feeling that we are the same person across time and space. In BIID a lifelong mismatch with the own body shape and the desired form is reported, but no experiences of altered agency or disembodiment. This may explain why, in the present experiment, the body switching tasks did not differentiate between persons with BIID and matched controls.

In conclusion**,** seven right-handed BIID individuals, who all desire a left leg amputation, showed only tendencies for shorter RTs to human figures with a left leg amputation. Thus, our hypothesis of a faster mental integration of pictures of a body shape compatible with one's desired shape could not be verified on statistical significance. However, we cannot exclude facilitated neurological processes to mentally transform perspectives of one's own body, possible due to lifelong mental imagery of a specific body shape or due to experience oneself in the desired body shape during pretending. Even an early ontogenetic under-representation of body-related brain processes in temporo-parietal regions cannot be excluded to have played a role in this process. Clearly in contradiction to our prediction, was the finding that the switching times between frequently and rarely presented stimuli were not enhanced in participants with BIID. This may disprove the idea of a generally attenuated cognitive ability to switch for persons with BIID and speaks against a prominent association between this condition and obsessive-compulsive traits.

2.3.3 Rubber Foot Illusion (RFI)

Introduction

The sense of body ownership describes the everyday feeling that our body belongs to us (Gallagher, 2000). This sense of belonging is mediated by the right hemisphere (overview see Keenan et al., 2005), as inferred by studies with patients with right-sided lesions, who often show an impaired sense of body ownership (e.g., in somatoparaphrenia; Feinberg & Keenan, 2005; Vallar & Ronchi, 2009). The sense of ownership builds, on the one side, upon the involvement of different sensations (bottom-up; e.g., vision, touch and proprioception), converging on a higher cognitive level and, on the other side, on our pre-existing cognitive representations of the body (top-down; Tsakiris & Haggard, 2005). Thus, ownership may involve multiple levels of multisensory matching of bottom-up and top-down processes (Botnivick & Cohen, 1998). Regarding BIID, researchers discuss whether a failure in this multisensory integration might underlie the disturbed feeling of ownership, leading to the strong feeling of non-belonging of one or more healthy limbs to their body. The experience of body ownership can be experimentally altered, e.g., in using the paradigm of the *rubber hand illusion* (RHI; Botvinick & Cohen, 1998). Thirteen years ago, the authors showed that healthy subjects felt a rubber hand as part of their own body after visual observation of irregular touches delivered to the rubber hand while their own invisible hand was synchronously touched at corresponding locations. This transient incorporation of an object into one’s own body schema is labeled the RHI. According to the authors “the effect reveals a three-way interaction between vision, touch and proprioception, and may supply evidence concerning the basis of bodily self-identification” (Botnivick & Chohen, 1998, p. 756). In the present study the RHI paradigm was modified for the use with persons with an amputation desire of the lower limbs.

In schizophrenic patients with reduced ownership ratings for a limb, the RHI was found to be larger than in healthy controls (Peled et al., 2000). Healthy people also differ in the susceptibility to experience a RHI, what is discussed to be due to different interpersonal components, as generally heightened illusion proneness (Mussap & Salton, 2006). A neural basis of the RHI has been related to activity in bilateral premotor cortex and inferior parietal lobe and their connections, providing a mechanism for bodily self-attribution (Ehrsson et al., 2004; Tsakiris, 2007, 2010; Zeller et al., 2011).

In this study we measured in individuals with BIID the size of the illusion for their non-desired foot compared to their normally integrated foot. This could offer information on a possible disruption of limb ownership and underlying multisensory processing. Because all our participants had an amputation desire for their leg, we accommodated the RHI paradigm for feet. To our knowledge this is the first time the rubber foot illusion (RFI) was conducted as well as in people with BIID. We established the size of the illusion with three standard methods that comprise (1) questionnaire responses, (2) the magnitude of *proprioceptive drift* and (3) skin temperature values. For the first method Botnivick and Cohen (1998) developed a self-rating questionnaire that is widely used and evaluates the perceived vividness of the RHI. The second method assesses the *proprioceptive drift* (Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005), i.e., the subjective displacement of one’s real, concealed limb towards the artificial one that is visually observed. The third method involves recording skin temperature during the evocation of the RFI. This method was introduced by Moseley et al. (2008), who showed that the stronger the RHI, the lower the temperature of the specific hand. These authors suggested temperature as a physiological correlate of limb disownership during the RHI. Other objective methods are used in studies for on the RHI, such as skin conductance responses (SCR) or neuroimaging approaches.

For our study we hypothesized that a possible multisensory deficit for the non-desired limb would lead to a larger RFI for the unwanted foot than for the accepted foot. First, we predicted an increased subjective vividness of the illusion for the unwanted foot as rated in the questionnaire. Second, we expected an increased proprioceptive drift in the felt position of the critical limb towards its rubber counterpart. And third, for the most direct physiological correlate of the illusion, skin temperature, we predicted a larger drop on the non-desired foot (compared to a baseline condition). Finally, we expected these three measurements to be mutually interdependent (i.e., positively correlated to one another; Moseley et al., 2008; Tsakiris & Haggard, 2005).

Subjects

All subjects with BIID and matched control participants took part in the experiment. Of the 15 subjects with BIID, we analyzed a homogenous subgroup of 8 right-handed and right-footed subjects with an enduring amputation desire of the left leg (mean age = 46.9 years, SD = 14.6 years; see participants #1-8 in table 3, p. 19) and their matched control subjects (mean age = 48.1 years, SD = 11.5 years). In the analysis of the third depended variable, temperature, one participant with BIID and his matched control subject were discarded due to an inexplicable drop of skin temperature on the left foot in the first part of the experiment.

Design and Procedure

The rubber foot paradigm was conducted in accordance with the experimental guidelines of Botnivick and Cohen (1998), Tsakiris and Haggard (2005) and Moseley et al. (2008). The subjects were tested in a sitting position, both feet placed on the floor. During the experiment the participants' feet were covered from view and only the rubber foot (either the right or left foot, depending on the condition), placed 20 cm to the subject's real foot was in view. The real and the rubber foot were stimulated and subjects were requested to observe the experimenters' paintbrush stroking on the rubber foot (for experimental arrangement see figure 7A,B). In the experimental condition the real foot and rubber foot were stimulated two minutes synchronously on identical parts of the foot using a paintbrush. In the control condition the real foot and rubber foot were stimulated asynchronously on different parts of the skin. The order of the resulting four conditions (left synchronous, right synchronous, left asynchronous, right asynchronous) was randomized and counterbalanced across participants. Each of these four conditions took approximately seven minutes to complete and included all three measurements described in detail below.

The size of the illusion was measured first, by questionnaire responses about the *perceived vividness* of illusion. After each of the four conditions, the participants had to evaluate 9 randomly presented questions (-3 for "strongly disagree" to +3 for "strongly agree"), whereof three questions were critical and six were control questions (Botnivick & Cohen, 1998; see table 11).

Table 11: Questionnaire for the rubber foot illusion experiment, including three critical questions (1-3) and six control questions (4-9).

1. Es kam mir vor, als ob ich die Berührungen des Pinsels dort spürte, wo ich sie auf dem Gummifuss sah
2. Es schien, als ob der Gummifuss mein eigener gewesen wäre
3. Es fühlte sich an, wie wenn sich mein richtiger Fuss zum Gummifuss hin verschoben hätte
4. Es schien, als ob ich mehr als einen linken (rechten) Fuss gehabt hätte
5. Es fühlte sich an, als würde mein richtiger Fuss irgendwie "gummig" werden
6. Es erschien (optisch), als ob sich der Gummifuss zu meinem richtigen Fuss hin verschoben hätte
7. Der Gummifuss begann im Aussehen (Form, Hautfarbe, Pigmentierung etc.) meinem eigenen zu ähneln
8. Es schien, als ob die verspürte Berührung von irgendwo zwischen dem richtigen Fuss und dem Gummifuss herkam
9. Es schien, als kämen die gespürten Berührungen vom Pinsel her, der den Gummifuss berührte

Second, we measured the magnitude of the *proprioceptive drift*, a drift towards the rubber hand when experiencing an illusion, modified by Tsakiris and Haggard (2005). We assessed proprioceptive drift by having the participant indicate the felt position of his invisible big toe by means of rulers with an arbitrary scaling. Thus, before and after each stimulation, the rubber foot was covered with a panel where four different rulers (in centimeters) were presented successively and directly above the covered real foot and rubber foot. The participants had to judge the location of the unseen big toe of the stimulated foot on each ruler (figure 7C). The judgments before the exposure to the rubber foot were the baseline and were subtracted from the judgments after the exposure. This difference resulted in the magnitude of proprioceptive drift (Tsakiris & Haggard, 2005). A training session before the experiment, judging 8 rulers for each foot, was excluded from analysis.
Third, we assessed the size of illusion measuring skin temperature on the foot, as introduced by Moseley et al. (2008). The temperature was assessed every 20 seconds on one site on both feet using infrared thermometry (IRtek, IR15, Australia; figure 7D). The values were measured simultaneously on each participant's foot (beside the ankle, on a non-stroked part of the foot) while one of the feet was stimulated. We sampled skin temperature values from the whole two-minute period of stimulation (6 succeeding measurements) and compared them to the baseline. In addition, room temperature from a thermometer was noted at about the same time points during the experimental session to control for temperature changes in the room.

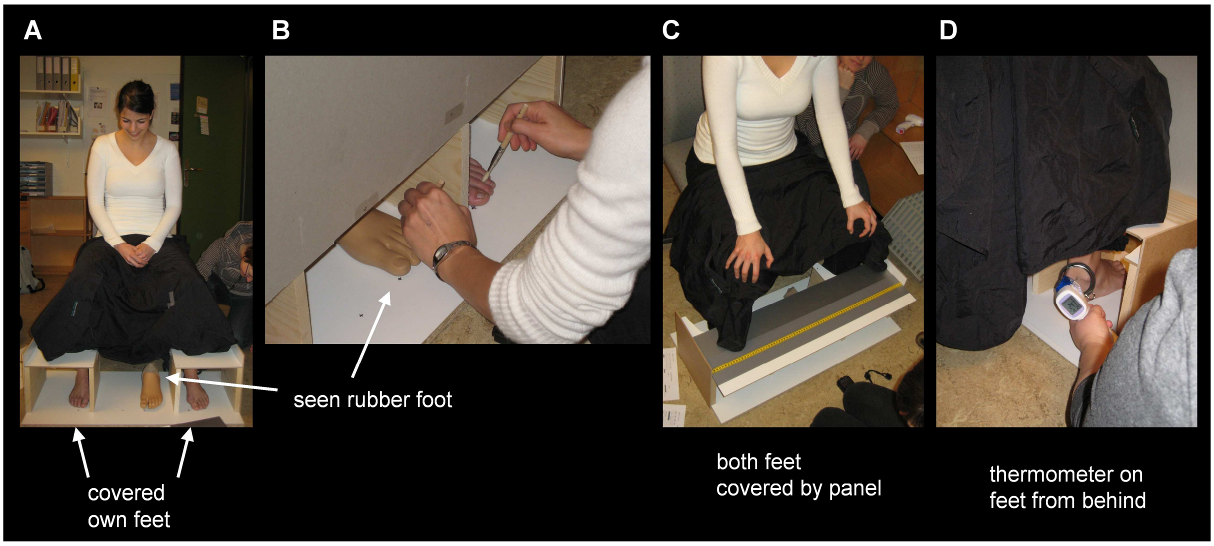


Figure 7: Experimental arrangement. A) shows a sitting participant with the covered own feet and a left rubber foot in view. Legs are covered by a black cloth to prevent them from view. In B) the left real foot and left rubber foot are asynchronously stimulated by using two paintbrushes. A grey pasteboard hides the arm movements of the experimenter. In C) the subject has to judge the location of the own big toe on presented rulers in order to measure proprioceptive drift. D) shows the measurement of skin temperature on the back of the feet (from behind) using an infrared thermometer.

Data analysis

Separate ANOVAs, for the three measurements: questionnaire, proprioceptive drift, skin temperature were calculated.

For the questionnaire data, the dependent variable *perceived vividness* of the illusion was analyzed using a three-way ANOVA comparing both groups for *foot* (unwanted left, accepted right) and *stimulation* (synchronous, asynchronous), as within-subject factors. Furthermore, two-way ANOVAs were separately performed for each group. To obtain an indicator of illusion, the dependent variable was weighted according to the mean of the control questions (4-9) subtracted from the experimental questions (1-3).

For the second dependent variable, *proprioceptive drift*, the same three-way ANOVA was performed for the within-subject factors *foot* and *stimulation* to compare both groups, as well as analyzing them separately for each group. To compose the proprioceptive drift, the ruler judgments before stimulation (baseline) were subtracted from those after stimulation.

Correlations between *proprioceptive drift* and *perceived illusion* were performed using Pearsons’ correlation.

For the third dependent variable, *temperature,* the data of seven participants with BIID and control subjects were analyzed. Here, the temperature values of the six measurements assessed during the rubber foot stimulation were compared to the corresponding baseline values of each of the four conditions. The temperature values taken from the feet that were stimulated were further analyzed (Moseley et al, 2008 showed that the effect was confined to the stroked hand and did not "spread" to the ipsilateral hand). In accordance with the other dependent variables, a three-way ANOVA was performed for the within-subject factors *foot* and *stimulation* to compare both groups, as well as two-way ANOVAs for both groups separately. The correlations between *temperature, perceived illusion* and *proprioceptive drift* were analyzed using Pearson’s correlation. Also using Pearson’s correlation, a possible relation between room and foot temperature was assessed. Furthermore, accuracy of the two thermometers was compared using nonparametric Wilcoxon test of simultaneous recorded test measurements (each 10 values) on both feet before the experiment started. All analyses were performed using SPSS 18 statistical software and Stat View 5.0.1.

Results

In short, the RHI experiment did not result in significant group differences or differences between both feet regarding the magnitude of the illusion (questionnaire, proprioceptive drift variables and temperature) of a subset with 8, respectively 7 participants with BIID. To control for an order effect of the four different randomized presented conditions, additional three-way ANOVAs were performed and revealed no significant order effect in all three methods.

Questionnaire

Analyses of the questionnaire measures reflect the magnitude of perceived vividness of illusion yielded no significant main factor *group* [$F(1, 14) = 0.117$, $p = 0.74$]. Furthermore, no significance for the interaction *foot x group* [$F(1, 14) = 0.26$, $p = 0.62$] or the main effect *foot* could be found [$F(1, 14) = 2.85$, $p = 0.114$] indicating that, against our first hypothesis, the BIID group did not perceiving the illusion differently from the control group. There was also no difference between the two feet. However, there was a main effect of *stimulation*

[F(1, 14) = 17.791, p = 0.001], in line with the literature. No significance was shown for the interactions *stimulation x group* [F(1, 14) = 0.199, p = 0.663] and *stimulation x foot* [F(1, 14) = 1.69, p = 0.215]. Another four-way ANOVA (*foot, type of question, stimulation*) was performed to analyze if the type of question (three experimental versus six control questions) differed. This analysis revealed a significant main effect *type of question* [F(1, 14) = 20.43, p = 0.000]. A three-way ANOVA for the groups separately, showed that individuals with BIID did not rate the perceived illusion differently for the two feet [F(1, 7) = 1.29, p = 0.293]. In contrast, the control group revealed a strong tendency to differentiate between both feet [F(1, 7) = 5.012, p = 0.060]. Specifically, the illusion was tendentially stronger for the left foot. Furthermore, the kind of stimulation significantly mattered for the group with BIID [F(1, 7) = 35.72, p = 0.001], such that synchronous stroking produced an illusion, but not asynchronous stroking. In the control group only a tendency in the same direction was observed [F(1, 7) = 4.197, p = 0.080]. For neither group was there a significant interaction *foot x stimulation* [BIID group: F(1, 7) = 0.914, p = 0.371; Control group: F(1, 7) = 0.893, p = 0.376] (figure 8).

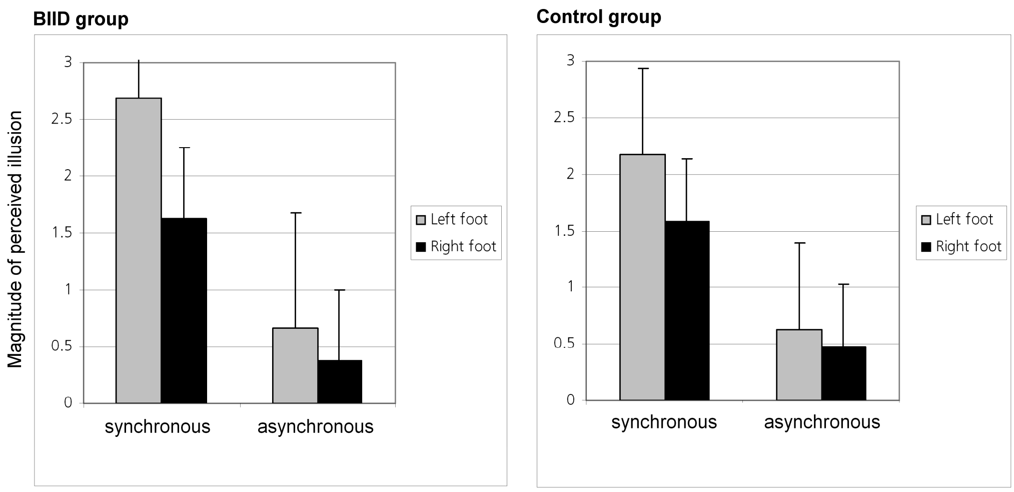


Figure 8: Interaction *foot x stimulation* for perceived vividness for each group: Mean of perceived vividness of illusion (-3 for "strongly disagree" to +3 for "strongly agree") by both groups for the left/unwanted (grey) and right/accepted foot (black), for both stimulation conditions (synchronous, asynchronous). The interaction *foot x stimulation* was not significant for both groups. Against the prediction, the left/unwanted foot did not reveal general significant higher illusion rates (p = 0.293) for the BIID group. In contrast, the control group had a tendency (p = 0.060) to differ between both limbs. As depicted, the synchronous stimulation yielded higher illusion judgments, which was significant for the BIID group (p = 0.001) and tendentially significant in the control group (p= .080).

Proprioceptive drift

The analysis of proprioceptive drift revealed only a modest trend for the main factor *group* [F(1, 14) = 3.048, p = 0.103]. Furthermore, there was no interaction *foot x group* [F(1, 14) = 1.15, p = 0.302], nor a main effect of *foot* [F(1, 14) = 2.13, p = 0.167]. Moreover, neither the main effect *stimulation* [F(1, 14) = 0.29, p = 0.598] nor its interactions with *group and foot* were significant. Analyzing the groups separately, "against our second hypothesis" no larger proprioceptive drift for the left, unwanted foot for the BIID group was shown. Furthermore, proprioceptive drift and perceived vividness did not correlate with one another. There was only a tendency for right foot stimulation for the group with BIID [r = 0.744, p = 0.055].

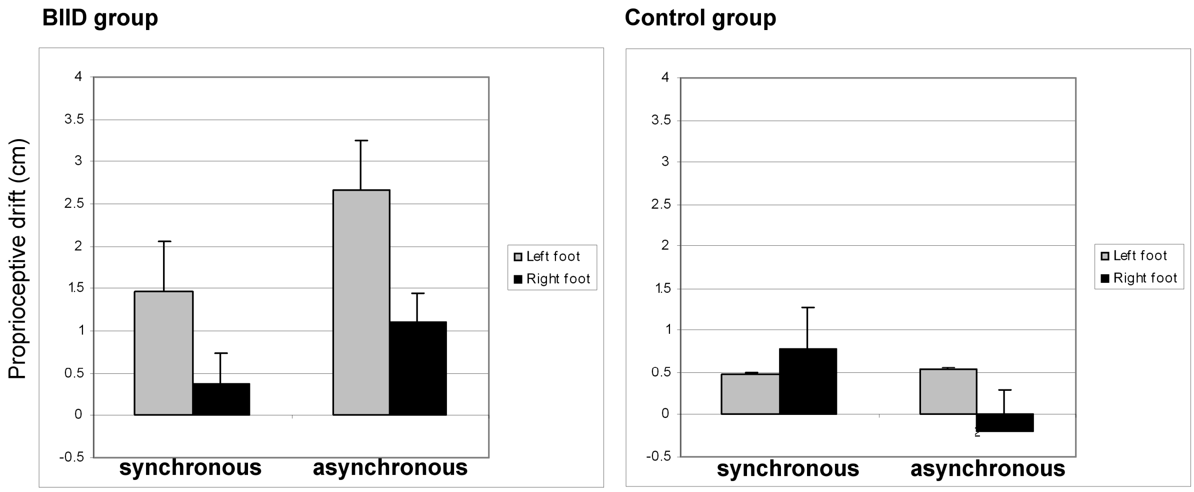


Figure 9: Interaction *foot x stimulation* for proprioceptive drift for each group: Mean of felt position of the invisible big toe towards the rubber foot (proprioceptive drift in cm). Bars in the positive range indicate a drift towards the rubber foot (indicator of RFI), bars in the negative range a drift away from the rubber foot (no RFI). The small trend of the group factor (p = 0.103) is visible, with stronger (but non-significant) proprioceptive drifts in the group with BIID (left panel) than in the control group (right panel). For the left foot (grey; Mean = 2.0 cm, SD = 3.2 cm), persons with BIID showed stronger positive drifts (not reaching any level of significance) towards the left than to the right rubber foot (black; Mean = 0.73 cm, SD = 1.9 cm).

Temperature

Compared to baseline, no significant change in foot temperature was found during the rubber foot experiment in either group. The temperature yielded no significant factor of *group* [F(1, 12) = 0.797, p = 0.39]. Moreover, there was no interaction *foot x group* [F(1, 12) = 0.56, p = 0.47], and no main effect for *foot* [F(1, 12) = 0.78, p = 0.785]. However, a slight trend for the interaction *foot x stimulation x group* was shown [F(1, 12) = 3.41, p = 0.090] (further analyzed below). Furthermore, the main effect *stimulation* was not significant [F(1, 12) = 0.913, p = 0.358] and no interaction for *foot x stimulation* [F(1, 12) = 1.55, p = 0.237] and for *stimulation x group* [F(1, 12) = 0.008, p = 0.930] were apparent.

Separate analyses of the groups did not reveal a main effect for *foot* or *stimulation*. The interaction *foot x stimulation* was just significant for the group with BIID [F(1, 6) = 5.907, p = 0.050], however; the temperature drops were obtained by both feet (see figure 10) and by both stimulations (e.g., temperature drops were larger for the left foot in the asynchronous condition and for the right foot in the synchronous condition). This interaction was not significant in the control group [F(1, 6) = 0.152, p = 0.710].

Changes of body temperature were not correlated with room temperature (r = 0.251, p = 0.181). Furthermore, the two infrared thermometers did not differ from each other prior to the stimulation (paired t-test: p = 0.564).

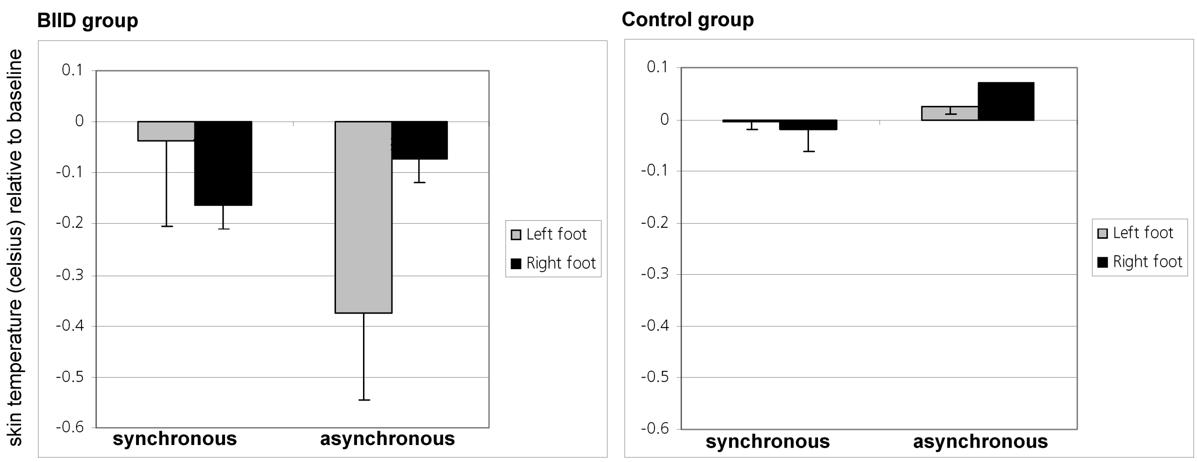


Figure 10: Interaction *foot x stimulation* for the variable temperature: Mean change in temperature compared to baseline for the two groups separately. Only in the group with BIID (left) the interaction was significant (p = 0.050). However, against our prediction, a drop in temperature was shown for both feet – the left/unwanted (grey) and the right/accepted foot (black). There were no temperature changes for the control group for both feet and both stimulations. Error bars represent standard errors of the mean.

Relating temperature changes with perceived vividness and proprioceptive drift

Correlating the temperature with the perceived illusion vividness according to the questionnaire, revealed only a significant relation for the left foot in the asynchronous stimulation [$r = 0.535$, $p = 0.049$; data over both groups]. This correlation fell short from significance in the control group [$r = 0.749$, $p = 0.053$], but did not show a trend in the group with BIID [$r = 0.174$, $p = 0.71$]. Temperature was not correlated with proprioceptive drift. Also, for the BIID group, with the largest proprioceptive drift and largest temperature drop in the left foot during the asynchronous condition (see figures 9 and 10), no intercorrelations could be found ($r \leq -0.142$, $p \geq 0.761$).

Discussion

In this experiment, we investigated the newly developed RFI in people with BIID and healthy controls to explore possible differences between the affected and the accepted foot in BIID. The majority of the participants verbally reported a RFI during the experiment. The illusion was quantified by three measurements, i.e., a self-rating questionnaire, a measure of proprioceptive drift and skin temperature changes on the foot. We predicted an elevated RFI (i.e., a sense of ownership) for the left rubber foot in people with BIID due to a hypothetically altered integration of proprioceptive, tactile and visual information concerning the critical leg.

First, how vividly the participants perceived the illusion was initially assessed by the questionnaire. Here, the group of left-leg BIID participants did not differ in perceiving the RFI from the control group. In contrast, the predicted stronger illusion for the left foot in the group with BIID was tendentially shown in the control group (for both stimulations). A larger illusion for the left hand compared to the right was previously reported by Ocklenburg et al. (2011). In that study, healthy participants experienced a RHI for the left hand (assessed by the same questionnaire) that was accompanied by stronger skin conductance responses (SCR) compared to the right hand. The authors proposed that this side effect could provide further evidence for a right-hemispheric lateralization of body ownership. Regarding this newly published study, our trends of a stronger left-sided illusion, in both groups and present in both stimulation conditions, could be related to neural mechanisms reinforcing an illusion experience of the left foot. Furthermore, our data showed that both groups perceived the vividness of the illusion stronger during synchronous stimulations – highly significant in the persons with BIID and tendentially in control subjects (Botnivick & Cohen, 1998). In summary, on the level of significance (neglecting the mentioned tendencies for a larger left foot illusion in both groups), our main hypothesis could not be verified as the group with BIID did not show a significantly stronger perceived illusion vividness for the left, unwanted foot.

Second, measuring proprioceptive drift revealed overall no significant main effects or interactions for either group. Thus, our second hypothesis has to be rejected as well (no increased magnitude of the proprioceptive drift for the unwanted left foot for people with BIID). The overall strongest trend was yielded for the between-factor group in showing more pronounced proprioceptive drifts for the group with BIID for both feet and stimulation types. Moreover, no correlations could be found proprioceptive drift and perceived vividness (questionnaire; see also Holmes et al., 2006) despite the frequently made claim that both measurements are associated (e.g., Tsakiris & Haggard, 2005).

Third, we monitored skin temperature on the foot as the most direct physiological correlate of the illusion (if present), in which negative drops had been associated with reduced ownership (Moseley et al., 2008). Altogether, similar to the proprioceptive drift analysis, the group with BIID showed larger, but non-significant, temperature drops during the rubber foot stimulation compared to control subjects. Within the group with BIID, a significant interaction of foot and stimulation was found. However, the temperature drops were shown for both feet and in both stimulations (more pronounced during asynchronous stroking). Thus, our third hypothesis also could not be verified (temperature drops were not larger for the left, unwanted foot in individuals with BIID). Relating temperature to the subjective ratings in the questionnaire and to the proprioceptive variable, revealed no notable correlations. This means that the temperature drops did not significantly relate to the individual magnitudes of the illusion, as Moseley et al. (2008) had shown in their rubber hand experiment. However, Ocklenburg et al. (2011) also failed to show a significant association between related illusion vividness and another physiological measure (SCR). It appears as if the verbal system parameter (questionnaire measure) is a poor indicator of changes on a purely physiological, or autonomous nervous system level.

Measurements of temperature have been described in clinical work, e.g., by Symons et al. (2001), who showed a breakdown in temperature regulation in 4 nonverbal, mentally retarded individuals. These breakdowns remained restricted to body parts frequently selected for physical auto-aggression, but did not affect control sites that were never injured. Thus, reduced homoeostatic control over body sites has been shown to be accompanied by self-injurious behavior (Mailis, 1996; Symons et al., 2001). Much earlier, experimentation in normal subjects had revealed an increase in blood perfusion in the hand that was attended to transiently (Patrizi, 1912). In our data, we could not find anomalies in temperature between the unwanted and the accepted foot that could be as a physiological correlate of limb disownership.

Under which circumstances limb ownership can be manipulated has been explored in several studies. For example, in using different rotations of the rubber hand to provoke a spatial mismatch and trying to evoke a RHI (Lloyd, 2007; Constantini & Haggard, 2007), or eliciting a RHI during movements (Kammers et al., 2009) it was shown that all these variables are critically involved in the illusion generation. Furthermore, enhancing illusory ownership of a rubber hand was achieved by left anodal galvanic vestibular stimulation (Lopez et al., 2010). However, incorporation of a wooden stick instead of a rubber hand into the body representation failed (Tsakiris & Haggard, 2005). In patients, the illusion of sensing touch on the rubber hand could be elicited in upper limb amputees by stimulating the stump (Ehrsson et al., 2008). In this context, we would like to mention a published review in collaboration with the University Hospital Balgrist (Curt, Yengue, Hilti & Brugger, 2010). We performed the rubber hand paradigm with a patient that experienced supernumerary phantom limbs of both arms after an incomplete spinal cord injury. The paradigm, applied for the first time in this clinical condition, elicited vivid supernumerary phantom limb sensations in a body posture (that is, sitting) that was normally not associated with spontaneous supernumerary limbs instead of an illusion of the real arm.

Taken all together the present study examines, for the first time, the rubber foot paradigm, exploring multisensory integration as the underlying mechanisms of body ownership in people with BIID who have the feeling of non-belonging of their left leg. In contrast to our hypothesis, the findings suggest that in people with BIID, the size of illusion for the left foot was not significantly increased whether assessed by subjectively reported vividness of the illusion (questionnaire) or by proprioceptive drift, or by skin temperature. Thus, our hypothesis of a pronounced plasticity of body ownership (due to altered integration of multisensory information) of the affected foot in people with BIID has to be rejected. Data showed comparable visuo-tactile-proprioceptive integration in people with BIID in both feet. Trends that did not reach statistical significance were shown in people with BIID having a larger proprioceptive drift and larger temperature drops compared to controls. However, these trends were obtained for both feet. Therefore, they indicate, if anything, an elevated RFI susceptibility for people with BIID, but no asymmetric RFI due to unilateral BIID.

2.3.4 Caloric Vestibular Stimulation (CVS)

Introduction

So far, therapeutic treatments to alleviate the amputation desire in BIID are scarce or ineffective. For example, psychotropic treatment was reported to have no relieving effect on the amputation desire (Bayne & Levy, 2005; Braam et al., 2006; First, 2005). In the present study, we explored a potentially alleviating effect on the amputation desire in using caloric vestibular stimulation (CVS) in persons with BIID. Clinically, CVS of the left ear with cold water alleviates left-sided neglect and related hemispatial deficits (Bottini et al., 1995). More intriguingly, non-spatial functions, such as the cognitive evaluation of one's health state and disturbances of corporeal awareness, can similarly be influenced by vestibular stimulation. Thus, anosognosia, i.e., the denial of illness, may disappear after cold water application to the left ear (Cappa et al., 1987). Most relevant for the present study is the observation that left-ear CVS with cold water also influences disturbances of body ownership. Thus, Bisiach et al. (1991) showed that somatoparaphrenic denial (i.e., the delusional belief of a disownership of body parts) could transiently be abolished in patients with right hemisphere lesions. It is thought that in these patients irrigation of the left ear activates the right damaged hemisphere since CVS is known to activate the contralateral hemisphere (Bottini et al., 1994; Vitte et al., 1996). Based on functional brain mapping, CVS induces activation in the insular gyrus, intraparietal sulcus, superior temporal gyrus, hippcompus, cingulate gyrus and thalamus (Suzuki et al., 2001). These cortical and subcortical regions are thought to include the vestibular cortex (homologues to the non-human primates *parieto-insular vestibular cortex*, PIVC; e.g., Grüsser et al., 1990).

As of today, it is not clear whether the modulating effect of vestibular balance only targets disorders of unilateral bodily functions (in particular hemiplegia) or whether vestibular-cognitive interactions encompass a much broader range of evaluative control of bodily function and the attribution of ownership to selected body parts (for a more general context of vestibular-cognitive interactions see Miller & Ngo, 2007). Ramachandran and Mc Geoch (2007b) suggested that left-ear caloric irrigation, through restoring body image integrity, might also alleviate the desire for limb amputation in BIID. We have explored this possibility empirically and hypothesized that left cold-water CVS will temporarily reduce the feeling of not belonging of the rejected limb, first inducing a subjective change in feeling of body ownership and second, an increase of skin temperature selective to the unintegrated limb (compared to a baseline condition) based on associations between local body temperature and degree of ownership of a limb (Moseley et al., 2008).

Subjects

Thirteen participants with BIID aged from 28 to 67 years (mean age = 48.3, SD = 13.1) and their age-matched control participants, aged from 34 to 64 years (mean age = 49.2, SD = 10.9) took part in the experiment. Of the 13 subjects with BIID, 8 had an enduring amputation desire of the left leg, 2 of the right leg and 3 subjects of both legs. Additionally, we separately analyzed a homogenous subgroup of the 8 right-handed and right-footed subjects with a left leg desire (see participants #1-8 in table 3, p. 19).

Design and Procedure

Prior to CVS, each participant underwent an otological examination to ensure an intact tympanic membrane and, if necessary, to clear the external auditory canal. Participants were lying during the CVS in supine position with the head inclined 30° from the horizontal (for methodological details of CVS see Jacobson & Newman, 1997). To verify successful vestibular stimulation, eye movements (particularly to observe nystagmus) were monitored with video-oculography (figure 11A). CVS with cold water (22°) was conducted during 4 minutes, counterbalanced for the left and right ear. Upon appearance of nystagmus, participants were asked to rate the actual *feeling of disturbance* for all four limbs on a visual analog scale from 0 (does not disturb me; no desire for amputation) to 10 (disturbs me extremely; intense desire for amputation) compared to the perceived ownership before the stimulation. These questions (feeling of disturbance) were asked in total 4 times during CVS (every 40 seconds) and once prior and once after CVS in a counterbalanced way. Simultaneous to the questions, skin temperatures was measured (again 4 times during CVS, once prior and after CVS) using infrared thermometry (IRtek, IR15, Australia). Temperature was recorded in a counterbalanced order on eight body locations (figure 11B and 11C), on each of the four limbs above and below the elbow, respectively knee (e.g., above and below the desired levels of amputation). After each of the two ear irrigations, participants were asked to retrospectively rate their vertigo and nausea perceived during CVS on a scale from 0 (no vertigo/nausea) to 10 (extreme vertigo/nausea). Between the two ear stimulations subjects rested for about 5-15 minutes until they felt no more discomfort caused by the stimulation.

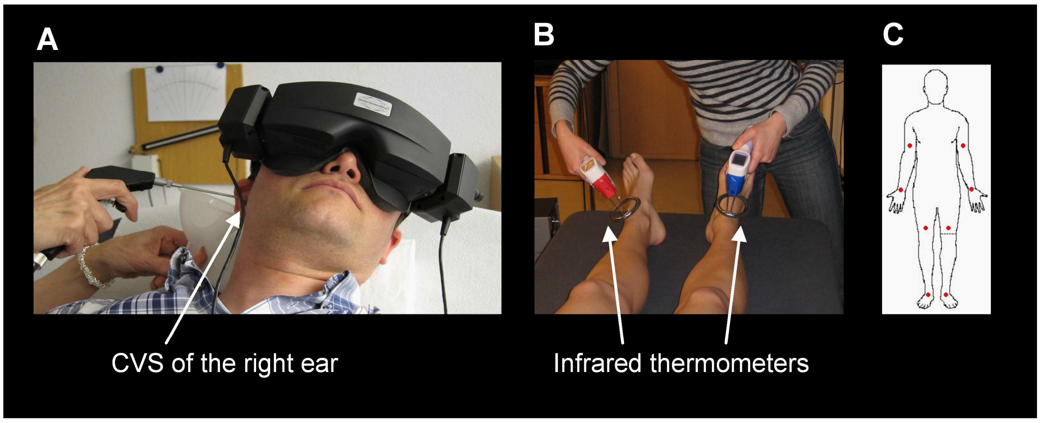


Figure 11: Experimental arrangement. A) shows right-ear CVS with 22° cold water. The subject wears goggles to record eye movements (particularly the nystagmus). In B) the temperature on the dorsal aspect of the two feet is measured simultaneously by two infrared thermometers. In C) the eight body locations (red dots) of recorded temperature values are displayed.

Data analysis

The verbally rated *feeling of disturbance* was analyzed by t-tests compared to the baseline (prior to the CVS), as well as with repeated measures ANOVA with *ear* (left, right CVS), *time* (5 time points relative to baseline), *side* (left, right) and *limb* (arm, leg) as within-subject factors and group (BIID, control) as between-subject factor.
For the temperature values, first the time course of the 5 succeeding time points of temperature recordings were subtracted from the baseline to reduce the amount of variables. Then, we performed repeated measures ANOVA, with *ear side*, *limb* and *location* (proximal, distal) as within-subject variables and group (BIID, control) as between-subject variable for all 13 subjects. These analyses were additionally performed for a homogenous group of 8 subjects with a left-leg amputation desire.
Moreover, Pearsons' correlations between room and body temperature were performed to control for a possible relation. In addition, control temperature values prior to each CVS measured by the two thermometers were compared using nonparametric Wilcoxon test. Finally, paired t-tests were calculated to compare the nystagmus during left and right CVS as

well as to compare perceived vertigo and nausea (self-rating scale) in both ear stimulations. All analyses were performed using SPSS 18 statistical software and Stat View 5.0.1.

Results

Persons with BIID reported no alleviation of the amputation desire or no alteration of bodily ownership during CVS of either ear. On average, BIID subjects rated their f*eeling of disturbance* related to the unaccepted limb at 4.5 (SD = 3.6) before and 4.8 (SD = 3.9) after CVS on the scale from 0 to 10. Corresponding ratings from control subject were 0, throughout. Repeated ANOVA with the conditions *ear, time, side* and *limb* revealed the expected, but trivial *group* effect [$F(1, 25) = 19.7$, $p = 0.000$] and a main effect of *limb* [$F(1, 25) = 11.85$, $p = 0.002$]. However, and contrary to our hypothesis, no effects of *time course* (e.g., alleviated amputation desire over time) or stimulated *ear* (predicted left ear CVS) were shown.

Analyzing skin temperature, no significant change in body temperature compared to baseline was found during CVS in either group. Repeated measures ANOVA performed with the conditions (ear, side, limb and location) revealed no significant *group* effect [$F(1,25) = 0.052$, $p = 0.822$], nor any main effects relevant to the hypothesis. Two triple interactions approached significance (1) *ear x limb x group* [$F(1,25) = 7.034$, $p = 0.014$], showing for both groups colder temperatures on the legs during left compared to right ear CVS, but an inverted relationship for the arms in control participants and (2) a significant interaction *limb x location x group* [$F(1,25) = 4.45$, $p = 0.046$], pointing to warmer temperatures for controls on proximal the legs, whereas subjects with BIID had warmer temperatures distally on the legs (see further analysis separately for each group in the next paragraph). Effects beyond the scope of immediate interest first revealed a main effect of *limb* [$F(1,25) = 7.66$, $p = 0.011$], pointing to warmer arms than legs, and a main effect of *location* [$F(1,25) = 13.45$, $p = 0.001$], showing that, overall, proximal locations were warmer than distal ones.
Analogous analyses performed for the two participants groups separately, revealed for the BIID group a trend for an interaction *limb x location* ($F(1, 12) = 4.16$, $p = 0.064$), pointed again to fact that the distally located feet were warmer than the thighs, whereas the distally located hands were colder than the upper arms. The control group showed several significant effects, such as a main effect for *limb* [$F(1, 12) = 7.39$, $p = 0.019$] and for *location*

[F(1, 12) = 28.79, p = 0.000], indicating the same regularities as described above (arms warmer, respectively proximal locations warmer). Additionally, in the control group a significant interaction *ear x limb* was shown [F(1, 12) = 13.296, p = 0.003], pointing to colder legs through left-ear CVS and finally a significant interaction *side x location* [F(1, 12) = 5.093, p = 0.043] without providing further relevant information.

The same five-way ANOVA obtained for the subgroup of 8 participants with a left-leg desire again produced no *group* effect. Three significant interactions involved the factor *group*: first, *limb x group* [F(1, 15) = 7.314, p = 0.017] indicating slightly colder arms in subjects with BIID and slightly colder legs in control subjects. Second, the significant interaction *ear x limb x group* [F(1, 12) = 6.43, p = 0.024] indicated – as in the larger sample – colder legs during left-ear CVS for both groups and slightly colder arms during right-ear CVS for the control group. Third, the scarcely significant interaction *side x limb x location x group* [F(1, 12) = 4.76 p = 0.047] showed overall warmer right sided locations for subjects with BIID and a mixed pattern in controls with warmer right legs and colder left arm locations. Close to significance was the interaction *location x group* [F(1, 12) = 4.403, p = 0.055].
In the analogues separate analysis for each group (n = 8), no significant effects or trends were shown for the group with BIID. Against our hypothesis, temperature did not differ on the critical left leg between the two locations (proximal and distal) or between both distal locations on the left and right foot (figure 12). In contrast, in the control group several significant effects were revealed again as shown in the previous section with the larger sample of 13 controls. In controls significant main effects of *limb* [F(1, 7) = 12.51, p = 0.010] and *location* [F(1, 7) = 29.86, p = 0.001] were evident. Further, the interaction *ear x limb* [F(1, 7) = 6.22, p = 0.041] and two additional interactions, *ear x side x limb* [F(1, 7) = 5.66, p = 0.049], and *side x limb x location* [F(1, 7) = 6.5, p = 0.038] were significant as well.

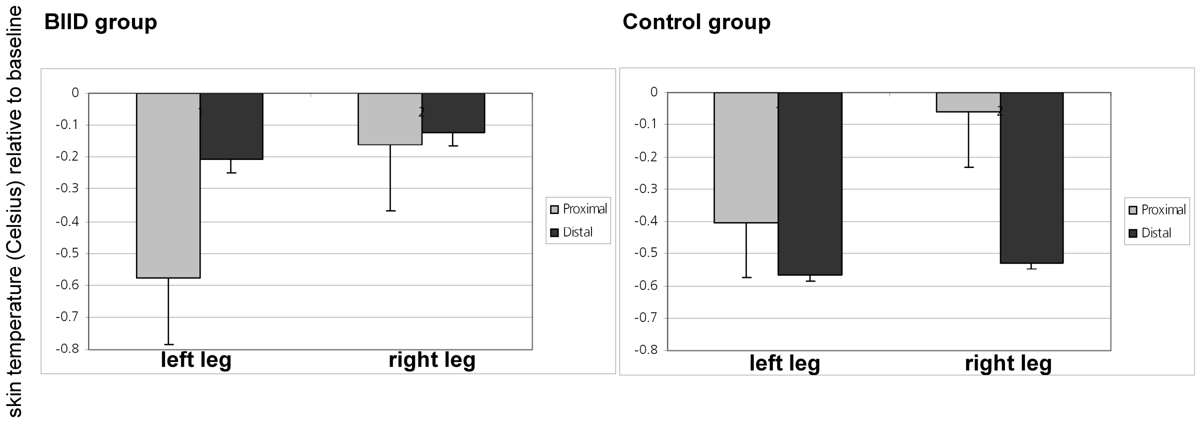


Figure 12: Interaction *side x limb x location* (here only for the legs) for the temperature measurements in each groups separately: Means of temperature drops compared to the baseline for both groups. The above shown interaction was only significant in the control group (right panel; p = 0.038). Against our prediction, in persons with BIID, no warmer temperature values on the left unwanted foot (bright grey) were shown during CVS. In contrast, the left foot turned to be colder during CVS (however, less than in the control group). Furthermore, in the group of BIID, no difference between the proximal (accepted body part; bright grey) and distal (unwanted body part; dark) part of the left leg was shown (intra-limb). As well as no difference between the left foot (distal part) and right foot (distal part) was revealed (inter-limb).

We correlated body temperature and room temperature to control for a relationship. Thus, in the control group (n = 13), body temperature was not correlated to room temperature (r = -0.23, p = 0.448), whereas in the BIID group a significant relation was found (r = -0.72, p = 0.005). Importantly, the two thermometers did not differ significantly from each other prior to the left- and right ear CVS (paired t-test: p = 0.879). Further, no difference was found between the nystagmus during left-ear CVS (mean of slow eye movement; SEM: +-25.6°, SD = 12.4°) and right-ear CVS (mean of SEM: +-27.1°, SD = 15.6°; paired t-test: p = 0.638). Finally, the perceived vertigo (self rating scale) did not differ in both CVS (paired t-test: p = 0.081), nor did nausea (p = 0.34).

Discussion

Our experiment demonstrates that persons with BIID reported no alleviation of the amputation desire and no alteration of bodily ownership during cold-water CVS of either ear. Furthermore, CVS did not induce a significant change in temperature of the undesired limb(s) in the BIID (nor in the control group). Such a change could have been expected a subjective alleviation of the amputation desire. The same results were revealed for a homogenous subgroup of persons with a left-sided amputation desire (n = 8) and the matched control group, as CVS did not selective change the temperature in the affected, respectively left foot. Thus, we could not find anomalies in temperature between the unwanted and accepted foot in persons with BIID that could be supposed as a physiological correlate of limb disownership (Moseley et al., 2008). Overall, it may appear puzzling that the control group (in the larger and smaller sample) showed more significant differences of temperature values depending on the stimulated ear, the side of body and locations. For example, in controls colder temperature values of the legs during left-ear CVS and colder arms during right-ear CVS were obtained (persons with BIID had both limbs colder during left-ear CVS). Thus, in contrast to the control group, our sample with persons with BIID appears to have more homogenous temperature values on all their limbs during left- and right ear CVS (Hilti et al., 2010).

In the literature, caloric or galvanic vestibular stimulation in healthy subjects may induce symptoms of depersonalization and derealization ("body feels different, separated from surroundings"). Lopez et al. (2008) argue that these techniques disturb the integration of multisensory bodily information (e.g., vestibular, visual, proprioceptive and tactile) converging in the vestibular cortex. Such mismatches could lead to the mentioned illusory bodily feelings (e.g., depersonalization) that also share aspects with out-of-body experiences (for an overview see Lopez et al., 2008). Additional to illusory own body perception of the whole body, CVS also interferes with those of specific body parts. For instance, the experience of phantom limb sensations were modified in patients with paraplegia (Le Chapelain et al., 2001) and temporarily evoked in amputees who did not previously experience such sensations (Andre et al., 2001). The latter authors assume a possible reconstruction of a memorized or innate body schema, releasing the experience of a phantom sensation. Thus, Lopez et al. (2008) suggest that CVS artificially triggers body part illusions through vestibular processing. In brain-damaged patients, an effect of CVS of body part ownership has been found in somatoparaphrenia. Here, left-ear caloric irrigation with cold water has been shown to influence disturbances of body ownership and alleviate somatoparaphrenic denial in patients with right hemisphere lesions. Assuming that BIID would constitute an equivalent to these experiences, the present study explored a postulation of Ramachandran and McGeoch (2007b), i.e., that CVS could make BIID disappear. They speculated that irrigation of the left ear could be used to treat BIID by activating disturbed right parietal projection areas of the vestibular system. Support for this hypothetical dysfunction was added by Giummarra et al. (under review a). They relate the fact that the large majority in BIID desire an amputation of the lower limbs to a vestibular dysfunction, as the vestibular cortex seems to be primarily connected with the lower limbs (proprioceptive information), rather than the hands (Lopez et al., 2008). In our study, however, in contradiction to the prediction of Ramachandran and McGeoch (2007b), we could not find such an altered ownership of the rejected body part in our sample with BIID. The observations of modulated body ownership in clinic and in healthy people, as well as the proposed disturbed functions in parietal lobe in BIID composed an encouraging basis to find similar alterations in people with BIID. However, the resemblance of disturbed ownership in BIID and that in somatoparaphrenia may be rather superficial (see Lawrence, 2009; Ramachandran et al., 2009). In most cases of somatoparaphrenia overt sensory or motor deficits in the involved body parts are evident (Vallar & Ronchi, 2009), whereas persons with BIID do not report similar disturbances (First, 2005). Furthermore, the former group denies an ownership, but does not express the desire of amputation as in the latter group. Our null finding is disappointing as it destroys the hopes for somewhat hastily offered "alternatives to amputation".

Taking all in consideration, we predicted an alleviation of the amputation desire in BIID on the basis of findings in neurological patients. However, our findings demonstrate that cold-water CVS does not alter subjective body ownership in people with BIID, whether assessed by subjective report or by an objective physiological temperature measurement. Thus, they discourage the usefulness of the procedure to alleviate the desire for limb amputation in persons with BIID. Other therapeutic approaches, such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation or deep brain stimulation may still be considered (Brugger, 2011; Giummarra et al., 2011).

2.3.5 Temporal Order Judgments

Imapaired spatial-temporal integration of touch in body integrity identity disorder (BIID)
Ayoama, A., Krummenacher, P., Palla, A., Hilti, L.M. & Brugger, P. Spatial Cognition and Computation (in press).

Abstract

Body integrity identity disorder (BIID) is a failure to integrate a fully functional limb into a coherent body schema. It manifests as the desire for amputation of the particular limb below an individually stable 'demarcation line'. Here we show, in five individuals with BIID, defective temporal order judgments to two tactile stimuli, one proximal, the other distal of the demarcation line. Spatio-temporal integration, known to be mediated by the parietal lobes, was biased towards the undesired body part, apparently capturing the individual's attention in a pathologically exaggerated way. This finding supports the view of BIID as a parietal lobe syndrome.

Introduction

For the present experiment we took advantage of the observation that many subjects with BIID report a clear and stable demarcation line between "accepted" and "rejected" areas of a limb. Pin-prick to these two different areas of the body reportedly elicit a differential response by the autonomic nervous system (Brang et al., 2008), but primary sensory and motor functions seem to be spared. On the background of this dissociation, i.e., spared primary somatosensory function versus deficient higher-order integration into body image, we planned to establish the spatial-temporal integration of touch stimuli to the legs in persons with BIID. It is known that this type of integrative process is not mediated by primary somatosensory cortex, but by several superordinate sites, such as secondary somatosensory cortex, posterior parietal cortex, inferior frontal cortex, probably in conjunction with subcortical regions, as basal ganglia and cerebellum (Lacruz et al., 1991; Pastor et al., 2004).We used the paradigm of tactile temporal order judgments (TOJ), which requires a subject to determine which one of two touch stimuli presented in close temporal succession had been applied first. The body locations selected for application of the paired stimuli were the two feet, the two thighs above the demarcation line, and two points equidistant from the demarcation line, one at a proximal, the other at a distal location (plus a mirrored placement of the tappers on the intact leg). Based on previous work in healthy volunteers, in which experimentally induced disownership of a limb influenced TOJ (Moseley et al., 2008) and several studies in populations with impaired sensorimotor functions (see Discussion section), we predicted a differential temporal integration of touch at locations on "accepted" versus "rejected" body sites.

Participants

Late delivery of the apparatus made it impossible to perform the experiment with all individuals with BIID. Therefore, only five persons with BIID participated (mean age of 46.2 years; SD = 15.6 years; see participants #6-9 and #11 in table 3, p. 19). All wanted to have one single limb amputated, four of them a left leg (3 were right-handed and right-footed, one was left-handed and left-footed) and one of them a right leg amputation (right-handed and -footed person). As this experiment was later performed as the other behavioral experiments, we consequently examined fewer participants.

Design and Procedure

A tactile controller (Heijo Research Electronics, UK) with two vibro-tactile solenoid tappers (contact area 7 mm^2) was used. There were 4 blocks of different tapper placements: (1) dorsum of the left and right feet (duplicating the procedure in Schicke & Röder, 2006), (2) proximal sites on the left and right thighs (10 cm below hip joint), (3) two sites 5 cm above and below the demarcation line and (4) two homologous sites on the accepted limb. Each block was preceded by a short run of practice trials, which were not analyzed. We will refer to conditions 1 and 2 as "across-limb" conditions and conditions 3 and 4 as "within-limb" conditions. Each block had 160 trials of two consecutive vibrotactile stimuli, each lasting 10 ms and separated by stimulus-onset-asynchronies (SOAs) of 15, 30, 60, 120 or 240 milliseconds (ms). In half the trials one tapper was leading, in the other half the other tapper. The interval between paired stimuli varied randomly between 2000 and 2500 ms.

Participants were seated comfortably, the feet held in parallel and 40 cm apart. They were blindfolded and wore earphones through which white noise was delivered to mask any sound from the tappers. Participants indicated by key press which of the two taps was felt first. The two response keys were placed horizontally in the across limb condition (left key for left leg first) and radially in the within limb condition (proximal key for proximal site first). Stimulus application and response collection was controlled by a Microsoft Visual C++ 2008 routine.

Data analysis

We analyzed, for the two conditions separately, the just noticeable difference (JND) between the two consecutive taps, as the obtained values could be compared with those known from thorough psychophysical experimentation also testing the feet (Schicke & Röder, 2006). We further analyzed the points of subjective simultaneity (PSS) derived from the probability curves of participants' responses. Curve fitting was performed on the trial-averaged individual data and grandaveraged data with a Cumulative Gaussian function (Optimization Toolbox for MATLAB). Paired t-tests were used throughout and all p-values are two-tailed, unless otherwise stated.

Results

In neither across-limb or within-limb conditions were the JND values significantly different from the value of 64 ms found in extensive psychophysical testing for the JND on the dorsal side of healthy subjects' (uncrossed) feet (Schicke & Röder, 2006, table 1); $t(df = 4) = 0.01$, $p = 0.95$ and $t(df = 4) = 1.61$, $p = 0.18$ for the two feet and two thighs, respectively and $t(df = 4) = 0.86$, $p = 0.43$ and $t(df = 4) = 1.39$, $p = 0.23$ for the foot-thigh comparison on the accepted and that on the rejected limb, respectively. In neither condition was a significant difference between the JND values on proximal compared to distal sites [($t(df = 4) = 2.48$, $p = 0.05$]) and on the accepted compared to the rejected leg [($t(df = 4) = 2.19$, $p = 0.05$)]. The response probability distributions as a function of stimulus interval are shown in figure 13 (across-limb conditions) and figure 14 (within-limb conditions). In the across-limb conditions PSS were not different from zero (i.e., objective simultaneity), neither at distal stimulation sites [feet; $t(df = 4) = 0.13$, $p = 0.9$] nor proximally [thighs; $t(df = 4) = 1.22$, $p = 0.25$]. PSS at proximal sites were not different from those at distal sites [$t(df = 4) =1.87$, $p = 0.13$]. A different picture emerged for the within-limb conditions (figure 14). While on the accepted (control) limb PSS was significantly shifted towards the distal site, i.e., were subjectively noted as occurring on the foot rather the thigh [t(df = 4) = 3.15, p = 0.05], on the rejected limb the contrary was the case, i.e., a significant shift towards the proximal site [t(df = 4) = 4.31, p = 0.01]. The two PSS-values were significantly different from one another [t(df = 4) = 5.55, p = 0.005].

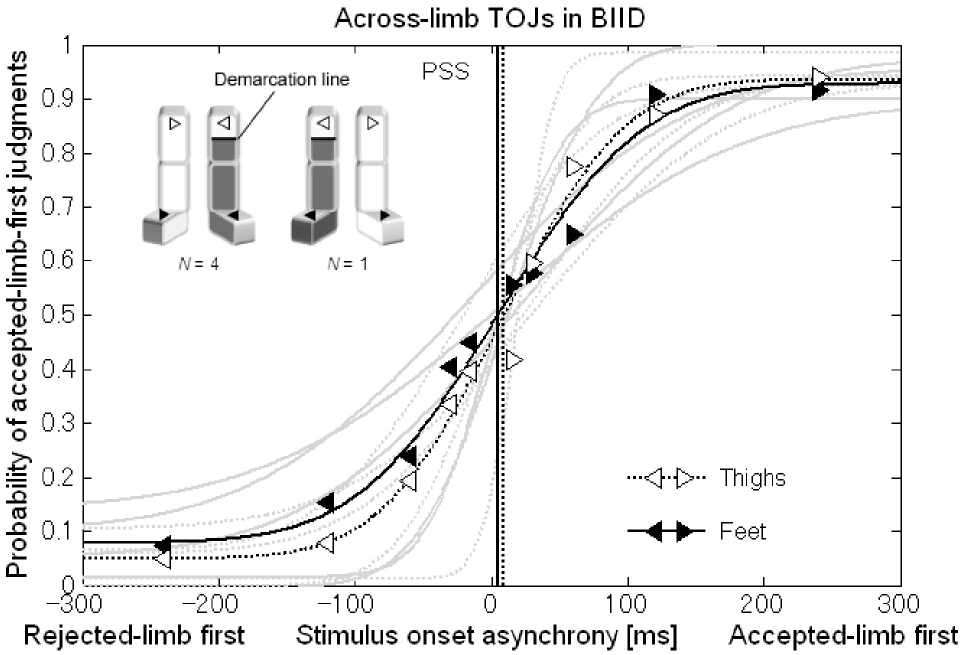


Figure 13: Probability curves of grand averaged (dark lines) and individual (light lines) TOJs of touch across limbs in BIID. Points of subjective simultaneity (PSS) for averaged TOJs are indicated by vertical lines. Each marker symbol represents a first stimulated site of a pair of taps, corresponding to the symbol in schematic illustrations of legs.

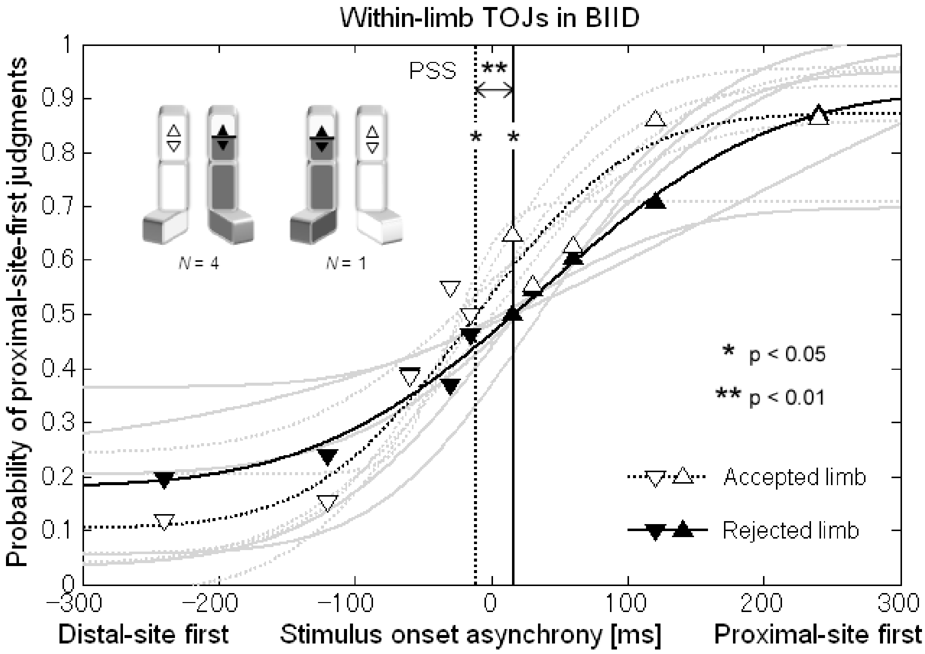


Figure 14: Probability curves of grand averaged (dark lines) and individual (light lines) TOJs of touch within a limb in BIID. Points of subjective simultaneity (PSS) for averaged TOJs are indicated by vertical lines. Each marker symbol represents a first stimulated site of a pair of taps, corresponding to the symbol in schematic illustrations of legs.

Discussion

In a small group of persons with BIID, who desire to have one of their legs amputated, we investigated the ability to differentiate which of two taps applied to two different sites on their body surface appeared first. Paired locations were the dorsal surface of both feet, and two corresponding sites on the thighs, i.e., two conditions which compared TOJs on the left versus right leg. A critical condition compared two locations with equal distance (5 cm) from the individual's demarcation line, separating accepted and rejected parts of the leg (the left in 4 cases, the right in 1 case). As a control condition we chose to stimulate mirrored sites on the accepted leg.

As a first finding and a prerequisite for the interpretation of BIID-related effects, we mention that the JND values obtained in the different conditions were not significantly different from the empirical values found by Schicke and Röder (2006) for healthy subjects' TOJ on the feet (i.e., 64 ms). The analogous condition in our experiment found an almost identical mean value of 63.8 ms (SD = 13.9 ms). Interestingly, the JND values found for the two thighs (mean = 47.4 ms, SD = 10.3 ms) were in the same order of magnitude (to give an impression of orders of magnitude, note the value of 160 ms found by Schicke and Röder (2006) for the stimulation of *crossed* feet). No significant differences emerged between the across-limb and within-limb comparisons or between accepted and rejected parts of the leg, which participants desired to have amputated.

With respect to the measure of PSS, the "points of subjective equality", we found an effect that we think constitutes the first-ever evidence for a psychophysical correlate of the desire of amputation. The mean SOAs between the two taps at which participants indicated that they felt the stimuli simultaneously (i.e., the PSS) were different when the two stimulation sites were equidistant from the demarcation line, that is the border between accepted and undesired body territory. Specifically, participants prioritized the tap on the distal, rejected part over that on the more proximal, accepted part. Conversely, on the control leg there was a significant prioritization of the proximal site, in accord with the shorter neural transmission times for proximal compared to distal stimulation sites.

This finding, that a body part, which is not accepted as an integral part of one's self, needs to be stimulated *after* that of a fully integrated part to generate the experience of simultaneity, comes as a surprise. Usually, for the PSS to be obtained, affected sensory fields needs to be stimulated *before* their unaffected counterparts. This is known from a variety of TOJ experiments in patient populations. In the visual modality, patients with extinction show a shift of the PSS towards the neglected visual field (Rorden et al., 1997). Likewise, tactile TOJ in patients with complex regional pain syndrome are also characterized by shifts of the PSS towards the painful side (Moseley et al., 2009). We could argue that in all these instances there is a marked sensory impairment; absence of phenomenal visual awareness during bilateral stimulation and continuous pain in one upper limb. This is not the case in our participants, who neither complain about sensory deficits nor have provided evidence for any abnormality in a thorough neurological examination. We would thus argue that their impairment is way beyond the level of primary somatosensory level, "more than skin deep", to paraphrase Longo et al. (2010), and involving secondary somatosensory cortex, fronto-parietal circuits (Blanke et al., 2009) and the insula (Brang et al., 2008). However, if the undesired body part is just underrepresented in body schema and thus not as much "present" despite normal sensor and motor functioning, some existing data on tactile TOJ still conflict with our observation of a shift of PSS towards the tap on the thigh. Moseley et al. (2008) induced the *rubber hand illusion* in healthy volunteers and subsequently assessed tactile TOJ on the hands (see chapter 2.3.3) This illusion is elicited by stroking one of the participant's unseen hands while simultaneously stroking a rubber hand, a procedure the participant has to visually observe. The illusion consists in an incorporation of the rubber hand and is paralleled by a *disownership* of the real hand. Consequently, Moseley et al. (2008) found that PSS after illusion induction were shifted towards the experimental, i.e., "disowned" hand. Moreover, vividness of the illusion was significantly correlated to the shift in PSS. We think that the apparent paradox between our findings and those by Moseley et al. (2008) is resolved once we recognize that in BIID the undesired limb is far from being "disowned" or "neglected". To the contrary, in fact, its mere physical presence constitutes a source of continuous attraction of attention. People with BIID are typically complaining that they feel "overcomplete" with the particular limb. Thus, rather than neglecting the unwanted limb, they show what has been labeled an "acute hemiconcern" (Bogousslavsky et al., 1995). This phenomenon, exclusively observed after stroke to the anterior parieto-temporal region of the right hemisphere, is a rare symptom involving a "feeling of strangeness" (Bogousslavsky et al., 1995, p. 428) in the contralesional half of the body (arm or leg). It is accompanied by an "overinterest" in the limb, but not a general attentional bias towards the contralesional hemispace. Acute hemiconcern finds a correspondence in healthy participants, who are presented with pictures of threat (especially of a physical nature) near a lateral body part and whose spatio-temporal integration is boosted after tactile stimulation of that body part (Van Damme et al., 2009). Shifts of the PSS towards the accepted part of a limb in persons with an amputation desire and away from a limb close to a threatening stimulus are further support that the deficit underlying BIID is not one depending on low-level somatosensory processing. What appears to be impaired are aspects of the body schema dealing with the affect-modulated binding of a body part into a corporeal *Gestalt*, evoking, in some individuals (Blanke et al., 2009) paraesthesias and related perceptual aberrations in a top-down way. Consistent with this view is the observation, in two individuals with BIID, that pin prick below the demarcation line led to an exaggerated autonomic response (heightened skin conductance response; Brang et al., 2008). We thus propose that the prioritization in our experiment of an undesired part of the body is due to a *hyperattention* directed towards that part. To further discriminate whether perception, attention and response production, is altered in BIID, future research on spatial-temporal integration of tactile information in BIID could employ paradigms asking for judgments of *simultaneity* rather than temporal order (Kuroki et al., 2010).

We agree with Brang et al. (2008) and McGeoch et al. (2011) to envisage the right superior parietal lobule and its connections with the insula as possible candidates for a seemingly bizarre disorder of corporeal awareness that may have innate components (Hilti & Brugger, 2010).

In opposition to the within-limb condition, where we stimulated accepted and rejected body sites closely adjacent on the skin, no comparable effects were found in the acrosslimb conditions of our experiment. Here, PSS were not different from zero (objective simultaneity), neither for thigh-thigh stimulations (both accepted body parts) nor for foot-foot stimulations (a comparison between an accepted and an undesired body part). In fact, for the latter comparison, the mean PSS we established (+1.0 ms, SD = 7.5 ms) again corresponded closely to the value found by Schicke and Röder (2006, p. 11810; mean = -5ms). It appears that bilateral stimulation can boost spatial-temporal integration over two sites with unequal representation in the body schema. This "bilateral effect" is reminiscent of recent findings by Tommerdahl et al. (2007), who experimentally impaired TOJ in healthy volunteers by the application of tactile vibration during the experiment. PSS was shifted only during stimulation of pairs of unilateral stimulus sites (two fingers of one hand), but not to bilateral stimulation sites (one finger of each hand). The authors interpreted this difference between unilateral and bilateral conditions by pointing out that in the former case the two touch signals reach adjacent cortex sites and the disturbing tactile noise would more readily hamper spatial-temporal integration than when two cortical sites in different hemispheres would be engaged with higher-order signal processing.

Some remarks with respect to the frequent claim, by persons with BIID, of an "eliciting event" for their amputation desire seem appropriate. In roughly half of the population studied (Brugger, 2011), we find descriptions involving a frequent exposure to the sight of amputees during early childhood. This exposure, also mentioned by three of our five participants (table 3) would have primed, if not directly triggered, the longing for being an amputee oneself. Although we are inclined to consider personal accounts of trigger events for BIID as retrospective constructions, we think it would be unwise to reject on an a priori basis the theoretical possibility of a highly emotional experience to cause some change in one's body schema, at least in susceptible persons.

In amputees, touch observed on other peoples' limbs can be "referred" to one's own corresponding phantom limb and felt as a tactile sensation (Fitzgibbon et al., 2010; Ramachandran & Brang, 2009). Interestingly, while the related phenomenon of "mirror-touch synaesthesia" in normally-limbed individuals is somatotopically organized (i.e., tactile stimuli to another person's arm are felt at one's *arm*), the referral in amputees is to the phantom limb, whether observed touch is directed to an arm or a leg (Giummarra et al., 2010; Goller et al., in press). In persons with BIID, observation of an amputee is likewise unspecific, i.e., in some cases the visual observation of an arm amputee is felt to have triggered the desire for a leg amputation (unpublished own data).

It would be premature to speculate further about possible candidate neural circuits involved in a hypothetical triggering mechanism for the desire for amputation. What is first and foremost needed is the recognition that the feeling of having a special body, however bizarre its manifestation can be accompanied by distinct alterations in bodily processing. BIID is more than just an Internet-propagated fad and also more than a purely "functional" psychiatric disorder in the traditional sense. Rather, as we attempted to show in the present preliminary experiment, careful tests of higher-order tactile processing may reveal a surprisingly basic dysfunction in the ability to integrate space and time on the skin.

Taken together, we showed in five individuals with BIID, defective temporal order judgments to two tactile stimuli, one proximal, the other distal of the demarcation line. Spatio-temporal integration, known to be mediated by the parietal lobes, was biased towards the undesired body part, apparently capturing the individual's attention in a pathologically exaggerated way Thus, the present finding supports the view of a disturbed parietal lobe function and other connected brain areas in BIID

2.4 Brain Imaging: Surface-based morphometry (SBM)

Abstract

Persons with BIID have the strong and enduring desire to have one or more healthy limbs amputated. To gain insights into the neuroarchitecture of this condition, the present study investigated, for the first time, possible grey matter anomalies in people with BIID. We acquired high-resolution T1-weighted magnetic resonance imaging scans from 13 men with BIID desiring amputation of one or both legs and 13 matched control persons. Using surface-based morphometry, we examined differences in cortical thickness, surface area and volume between the groups. We focused on right parietal, insular and subcortical areas, known to process low- and high level information about body parts including legs. Persons with BIID had significantly reduced cortical grey matter area in the right primary and secondary somatosensory cortex (SI, SII) and in the right anterior insula as well as decreased cortical thickness in the right superior parietal lobe (SPL). In addition, persons with BIID showed a reduced volume in both putamina. The observed differences between persons with BIID and controls may indicate altered networks for processing both low-level sensory information and higher-order body-related integrative functions. These networks comprise (1) a diminished limb representation in the right SI, SII and in bilateral putamina, (2) a disturbed multisensory integration of the affected limb in the right SPL and (3) altered mediation of emotional connotations of the affected limb in the anterior insula. Together, these alterations might lead to the feeling of non-belonging of the affected limb and therefore to the desire for healthy limb amputation.

Introduction

The neural mechanisms mediating corporeal awareness are not fully understood. From clinical incidents, such as strokes or tumours, we know several conditions of disturbed corporeal awareness (for an overview see Vignemont, 2010). Examples comprise bodily disturbances, in which patients no longer feel localized or embodied within their given physical body, as in *somatoparaphrenia* (Bottini et al., 2002; Gerstmann, 1942; Vallar & Ronchi, 2009) or in *asomatognosia* (Arzy, et al., 2006). In these conditions the right parietal lobe – the dominant site of body processing (e.g., Coghill et al., 2001) – is often disturbed.

Besides the right parietal lobe, other brain regions such as the premotor cortex and, the insula, which are connected with the parietal lobe, are considered to be involved in the generation of such bodily disturbances (overview see Berlucchi & Aglioti, 2010). Note that the *left* parietal lobe is also involved in disturbances of corporeal awareness, such as *autotopagnosia* (i.e., inability to localize and orient different parts of the body), *finger agnosia* (i.e., inability to distinguish the fingers on the hand) and *left right disorientation*in (i.e., inability to distinguish right from left). These mechanisms seem to be mainly associated to linguistic representations of body part (Berlucchi & Aglioti, 1997; Sirigu et al., 1991).

Qualitative similarities between disorders of the *right* parietal lobe and BIID (e.g., BIID as a chronic form of asomatognosia; Blanke et al., 2009), has lead to the assumption that also in BIID the right parietal lobe – especially the multisensory integration areas of the right superior parietal lobule (SPL) – may contribute to the development of disturbed body integrity (e.g., Brang et al., 2008; McGeoch et al., 2011). The recently published study of McGeoch et al. (2011) is the first and apart from ours', the only brain imaging study in individuals with BIID. As already mentioned in the *general introduction* (chapter 1.2.3) they used MEG in four individuals with BIID (two right, one left and one bilateral leg amputation desire). By touching their critical leg(s) compared to their accepted leg a significantly reduced activation in the right SPL was revealed in the former event. In control subjects the right and left SPL were equally activated upon touches to both legs. Other regions of interest (SI, MI, insula, premotor cortex, inferior parietal lobe and precunues) in both hemispheres did not show significantly different activations in people with BIID upon touches on both legs. McGeoch and colleagues (2011) proposed that the right SPL seems to be ideally located to integrate multisensory information (e.g., tactile, spatial, visual; see also Giummarra et al., 2008) and to build a higher-ordered body map (e.g., Stein, 1989; Wolpert et al., 1998). In BIID, the observed inactivation of the right SPL might reflect a disturbed integration of the affected limb. Persons with BIID could therefore experience the bizarre consequence of feeling touch on their unwanted limb (due to the normally received somatosensory signals), but without having the corresponding higher-order limb representation in the SPL coactivated.

Similar to McGeoch and colleagues we hypothesized that BIID reflects a disturbed integration of multisensory information of the affected limb(s) into a coherent cerebral representation of one's own body (Blanke et al., 2009). Thus, the purpose of our magnetic resonance imaging (MRI) study was to discover possible structural brain differences in grey matter in people with BIID compared to controls, and to discuss whether these morphological differences could be related to the non-desired limb(s) in BIID. We hypothesized, in accordance with Blanke et al. (2009) and McGeoch et al. (2011), a neurological basis of BIID that consists in a deficient representation of one or more particular limbs. This mis-representation could lead to the strong feeling of non-belonging of these limbs. We predicted structural differences in wide networks in the right hemisphere that are particularly associated with representations and multisensory integration of body parts, specifically the legs. Particularly, we expected alterations of the leg representation in the parietal lobe, processing low-level information and higher-order integrative functions (e.g., Kell et al., 2005; McGeoch, et al., 2011). Furthermore, in subcortical structures, such as the basal ganglia, such altered information concerning the affected leg was expected (e.g., Gerardin et al., 2003). And finally, on a higher-order level, we predicted differences in the insular cortex known to mediate emotional connotations of a limb and to guarantee the feeling of ownership (Brang et al., 2008; Craig, 2002; 2009).

Subjects

Thirteen participants with BIID aged from 28-73 years with a mean age of 49.3 (SD = 14.5 years) and their matched control participants, aged from 34-73 years (mean age = 50.2 years, SD = 12.5 years) took part in the MRI investigation. Of the 13 individuals with BIID desired a leg amputation, 8 had an enduring amputation desire for the left leg, 2 of the right leg and 2 aimed at a bilateral leg amputation. One person had an amputation desire mainly for the left leg, but also, however less intense, for an additional right leg amputation on the same level. Of the initially 15 recruited individuals with BIID, two could not be scanned because of physical unsuitability for the MRI investigation (metal in the eye, respectively too large head).

MRI data acquisition

We acquired structural T1-weighted MRI scans to investigate cortical and subcortical features of grey matter tissue. Imaging data were acquired using a 3.0 T Philips Achieva whole body scanner (Philips Medical Systems, Best, The Netherlands), located at the University Hospital Zurich and equipped with a transmit-receive body coil and a 16 elements SENSE (sensitivity encoding) head coil array. From all 26 participants a volumetric 3-D T1-weighted gradient echo sequence (fast field echo) scan was obtained with a measured and reconstructed spatial resolution of 0.94 x 0.94 x 1.0 mm^3 (acquisition matrix 256 x 256 pixels, 160 slices). Further imaging parameters were: Field of View (FOV) = 240 x 240 mm^2, echo-time (TE) = 3.7 ms, repetition time (TR) = 8.06 ms, flip-angle = 8°.

Note that also diffusion tensor imaging (DTI) scans were performed to examine white matter integrity, as well as resting state functional MRI (fMRI) to investigate connectivity. These findings will be communicated separately in a peer-reviewed journal. We first expected to find differences in fractional anisotropy (FA) between both groups and focused on parieto-frontal connections (Blanke et al., 2009; Brang et al., 2008; Craig, 2002; 2009) and on white matter adjacent to grey matter areas associated with body representation. Second, we expected to find group differences in the efficiency of body-related neural networks.

Surface-based morphometry

The origin of the coordinate system was manually set on the anterior commissure using SPM8 (Statistical Parametric Mapping 8) software, which is freely available for download online (http://www.fil.ion.ucl.ac.uk/spm) and is running under MATLAB (Link). Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Jovicich et al., 2006; Han et al., 2006; Fischl et al., 2004). Briefly, this processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles; Fischl et al., 2004; Fischl et al., 2002), intensity normalization (Sled et al., 1998), tessellation of the grey matter/white matter boundary, including automated topology correction (Fischl et al., 2001; Segonne et al., 2007) and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Fischl & Dale, 2000; Dale et al., 1999; Dale & Sereno, 1993). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999), registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999) and parcellation of the cerebral cortex into units based on gyral and sulcal structure (Segonne et al., 2004; Desikan et al., 2006; Destrieux et al., 2010). This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analyses (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). Data were resampled for all subjects into a common spherical coordinate system. The data were then smoothed on the surface tessellation using an iterative nearest-neighbor averaging procedure. 50 iterations were applied, equivalent to applying a two-dimensional Gaussian smoothing kernel along the cortical surface with a full-width-at-half-maximum of about 13 mm.

Data analysis

We computed a whole brain analysis to find differences in cortical surface area, cortical thickness and cortical volume between BIID and control subjects. The analysis of subcortical volumes was simultaneously controlled for total gray matter volume. Because this is the first structural brain imaging study examining people with BIID, we focused on our a-priori hypotheses targeting areas related to higher-ordered body representation such as the parietal and insular lobe. Furthermore, we also considered areas of lower-order leg representation, such as the primary and secondary somatosensory cortices and subcortical structures such as the basal ganglia (Berlucchi & Aglioti, 1997, 2010; Brang, et al., 2008; McGeoch, et al., 2011). To examine differences between the two groups, we used independent sample t-tests with a height threshold of $P < 0.01$ and a cluster extent threshold of 50 mm^2 vertices for the whole brain, uncorrected for multiple comparisons.

Results

Global brain measurements

No left and right hemispheric differences in cortical surface areas, cortical thickness or cortical volume were found between the groups. Moreover, there were no group differences in total volume, intracranial volume and subcortical grey matter volume as well as between left- and right hemispheric white matter volume. Finally, the experimental and the control group were also comparable in the relevant structural parameters with respect to age and education level (table 12).

Table 12: Demographic characteristics and global brain measurements of the left (L) and right cortices (R) of participants with BIID and healthy control participants.

	Participants with BIID (*n* = 13)		Control participants (*n* = 13)		Statistics	
	Mean	SD	Mean	SD	T(df = 24)	p-value
Age [years]	49.3	14.5	50.2	12.5	-0.17	0.86
Education [years]	15.4	3.0	14.7	2.9	.060	0.55
Intracranial volume mean [cm^3]	1509.3	218.1	1510.2	172.1	-0.12	0.99
White matter volume [cm^3]						
Total L	263.8	21.1	258.8	23.5	0.58	0.57
Total R	262.0	24.5	259.1	24.0	0.30	0.76
Subcortical grey matter mean [cm^3]	185.5	13.8	178.8	23.1	0.90	0.38
Cortical surface area [cm^2]						
Total L	856.9	52.9	849.3	60.5	0.34	0.74
Total R	849.4	59.5	848.0	59.9	0.59	0.95
Cortical thickness [mm]						
Mean L	2.462	0.11	2.452	0.078	0.27	0.79
Mean R	2.479	0.115	2.473	0.079	0.14	0.89
Cortical volume [cm^3]						
Total L	232.8	16.9	227.7	20.3	0.70	0.49
Total R	232.0	18.3	228.8	19.8	0.44	0.66

Surface-based measurements

Several predicted regions with significant morphological differences were revealed in the right parietal lobe (figure 15 and table 13). In the right SPL, a cluster with significantly reduced cortical thickness and cortical volume was found for the group with BIID (figure 15A; MNI coordinates of peak: x = 17, y = -50, z = 61). On the medial side of the right parietal lobe, a significantly smaller cortical surface area for the BIID group was obtained in the paracentral gyrus and sulcus, where the primary somatosensory representation of the left leg is located (figure 15C; x = 5, y = -38, z = 62). Furthermore, a smaller cortical surface area in participants with BIID was revealed in subcentral cortex/parietal operculum, located in the secondary somatosensory cortex (SII; figure 15B; x = 54, y = -3, z = 9). In another right hemispheric region of high interest, the right insular cortex (AIC)/frontal operculum, a smaller cortical surface area was found in the anterior part of the right insula for the group with BIID (figure 15B; x = 32, y = 25, z = 9). A second, smaller cortical area in the anterior insular cortex could be detected for BIID participants (figure 15B; x = 32, y = 20, z = -4), however, its cluster size of 44.7 mm^2 is slightly below the reported cluster extent threshold of 50 mm^2. In addition, we found reduced volumes of both putamina in the group with BIID compared with control males. A classical voxel-based morphometry revealed a cluster with reduced grey matter density in a region of the left putamen (x = -32, y = -1, z = 4) housing somatotopic representations of the body.

Table 13: SBM results: predicted significant clusters in the right hemisphere for subjects with BIID > control subjects (only clusters > 50 mm^2 considered).

Measure and anatomical location	Figure	Hemi-sphere	Cluster size (mm^2) in/decreased (+)/(-) for BIID group	Number of vertices	MNI coordinates x	y	z	p-value (df = 24)
Cortical thickness								
Superior parietal cortex (SPL)	15A	Right	58.2 (-)	115	17	-50	61	0.0013
Cortical area								
Anterior insular cortex (AIC)	15B	Right	87.3 (-)	208	32	25	9	0.0005
Paracentral cortex (SI)	15C	Right	62.8 (-)	167	5	-38	62	0.0025
Subcentral cortex (SII)	15B	Right	51.5 (-)	108	54	-3	9	0.0037
Cortical volume								
Superior parietal cortex (SPL)	15D	Right	51.2 (-)	104	16	-50	61	0.0018

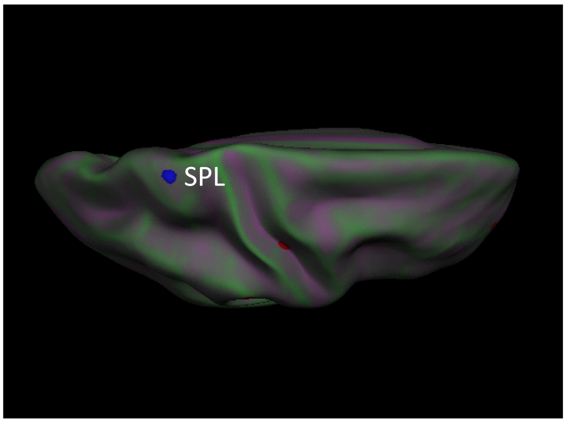
There were also anatomical differences in right parietal areas which process bodily information, but for which we do not have a priori hypotheses for BIID (see table 14). Thus, in the inferior parietal lobule increased cortical thickness was found for BIID participants (x = 57, y = -27, z = 38) as well as a larger cortical surface area for the same group, partly located in the inferior parietal lobe and partly in the superior temporal cortex. There was also a smaller cortical area in participants with BIID in the postcentral sulcus (figure 15B; x = 35, y = -31, z = 42) and larger cortical thickness and volume values within the central sulcus (figure 15A, cortical thickness: x = 33, y = -16, z = 40; cortical volume: x = 34, y = -18, z = 39). Furthermore, unexpected areas for which we did not formulate a priori hypotheses were found in right hemisphere cortex, left hemisphere cortex as well as in subcortical regions (e.g., smaller right nucleus accumbens and a smaller right hippocampus for the participants with BIID).

Table 14: SBM results: unpredicted clusters of the right and left hemisphere for subjects with BIID > control subjects (only clusters > 50 mm^2 considered).

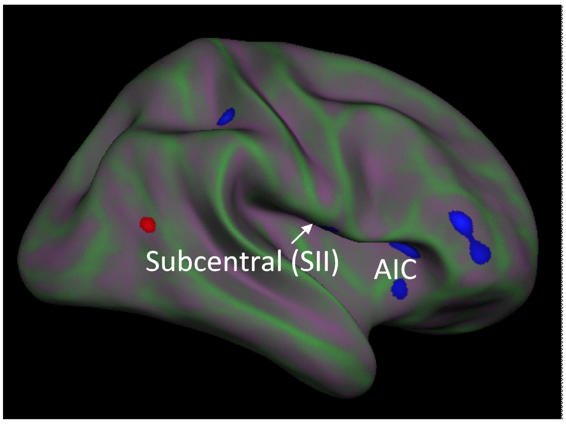
Measure and anatomical location	Figure	Hemi-sphere	Cluster size (mm^2) in/decreased (+)/(-) for BIID group	Number of vertices	MNI coordinates x	y	z	p-value (df = 24)
Cortical thickness								
Inferior parietal cortex	NS	Right	97.4 (+)	235	57	-27	38	0.0027
Inferior temporal gyrus	NS	Right	63.4 (+)	96	54	-26	-22	0.0033
Central Sulcus	15A	Right	58.5 (+)	125	33	-16	40	0.0054
Cortical area								
Pericallosal sulcus	15C	Right	76.1 (-)	233	7	-44	15	0.0002
Postcentral sulcus	15B	Right	63.5 (-)	158	35	-31	42	0.0005
Lateral orbitofrontal gyrus	15B	Right	265.8 (-)	339	40	34	10	0.0006
Superior frontal gyrus	15C	Right	90.4 (+)	146	8	36	37	0.0007
Temporal polar gyrus	15C	Right	118.7 (+)	229	28	1	-26	0.0008
Superior temporal sulcus	15B	Right	61 (+)	124	48	-56	15	0.0019
Pericallosal sulcus	15C	Right	51.5 (+)	121	4	7	25	0.0070
Superior temporal gyrus	15B	Left	149.2 (-)	364	-45	-26	7	0.0005
Inferior parietal gyrus	NS	Left	71.8 (+)	152	-61	-26	22	0.0028
Temporal Pole	15C	Left	63.8 (-)	121	-29	12	-34	0.0039
Middle temporal gyrus	NS	Left	123.2 (+)	178	-62	-18	-16	0.0049
Cortical volume								
Central Sulcus	15D	Right	182.7 (+)	351	34	-18	39	0.0026
Middle frontal gyrus	15D	Right	86.6 (+)	100	25	49	-2	0.0036
Middle anterior cingulate cortex	15D	Right	69.5 (+)	150	9	5	36	0.0054
Temporal polar gyrus	NS	Right	86.5 (+)	190	56	-33	33	0.0067
Rectal gyrus	NS	Left	95.2 (+)	160	-4	29	-20	0.0012
Inferior temporal gyrus	NS	Left	113.4 (+)	141	-51	-53	-12	0.0015
Inferior parietal gyrus	NS	Left	60.3 (-)	114	-41	-67	39	0.0020

NS = not shown

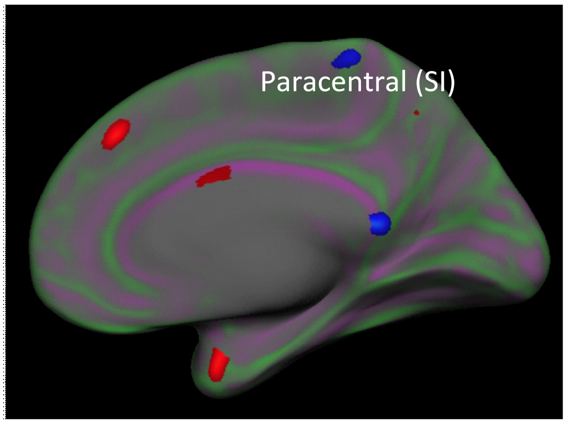
A Cortical Thickness



B CorticalArea



C



D Cortical Volume

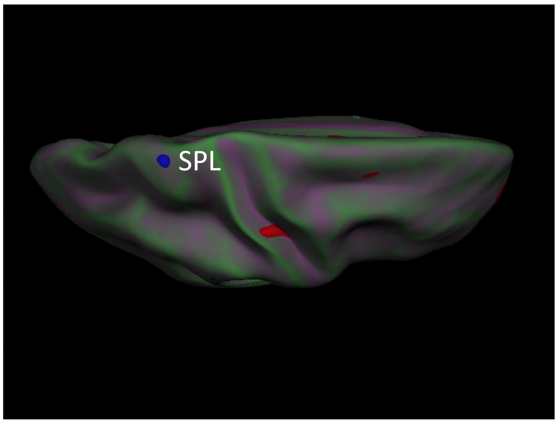


Figure 15 A-D: Statistical parametric maps of the surface-based morphometry. Blue clusters show reduced cortical size and red clusters show increased cortical size for the BIID group compared to the control group. Shown are predicted clusters (labeled) and nonpredicted clusters of (A) increased cortical thickness, (B and C) cortical surface area and (D) cortical volume in the group with BIID compared to controls, located in the superior parietal lobe, the paracentral cortex (SI), the subcentral cortex (SII) and the anterior insular cortex (AIC) (summarized in table 13). Statistical paramentric maps were projected onto the mean cortical surface of the 26 subjects and thresholded with $P < 0.01$ uncorrected for multiple comparisons.

Discussion

This study presents, to the best of our knowledge for the first time, grey matter anomalies in persons with BIID compared with healthy controls using structural MRI. We suggest a pattern of neuroanatomical differences in a network of cortical and subcortical regions processing both low level sensory information about feet or legs (we compared our results with data of feet representations as they are more frequently reported in literature than leg representations) and higher-order integrative functions. Specifically, this altered network comprises a diminished foot representation in the right SI and SII with reduced cortical surface area and reduced volume in bilateral putamina. Moreover, decreased cortical thickness was found in the right SPL, supporting recent findings by McGeoch et al. (2011) with MEG and indicating a disturbed multisensory integration. Finally, the proposed network involves a reduced cortical surface area in the right AIC, which is associated with an altered mediation of emotional connotations of the affected limb. This area has been previously implicated to be altered in BIID (Brang et al., 2008).

Taken together, these alterations might lead to the feeling of non-belonging of the affected limb in BIID. However, we can only speculate whether they are the cause or an effect of BIID or a mixture of both. To cite Oddo et al. (2009, p. 239) “whatever the direction is, it seems clear that BIID is early imprinted in the brain.”

In the following paragraphs we more closely discuss the five predicted findings as well as one unpredicted finding and propose their role and function in the genesis of BIID.

Primary somatosensory cortex (SI)

On a low cortical level, a smaller surface area in the group with BIID was found, located in the right paracentral cortex in the interhemispheric fissure of the right parietal lobe. This area is classified as belonging to SI and may reflect the contralateral somatosensory leg or foot representation (Penfield & Rasmussen, 1950). Compared to our finding (MNI coordinates: x = 5, y = -38, z = 62), similar coordinates following hallux (big-toe) stimulation were obtained in fMRI studies by Kell et al. (2005; Talairach coordinates of left toe: x= 12, y = -39, z = 72) and Michels et al. (2010; Talairach coordinates of right toe: x = -10, y = -44, z = 62). These data suggest that our finding in this region represents the left foot area of SI as well. The right but not the left hemispheric finding may reflect the desired amputation of the left leg in all participants of the BIID group, except in two participants desiring a right leg amputation.

What could a smaller cortical surface area imply? From an anatomical view, the smaller SI area of the left foot might indicate less cortical columns in this area, with a decreased arborisation per neuron, smaller glial volume or decreased regional vasculature. Up to date, not much is known about structural differences in cortical layers and columns and their relation to brain function and pathology. Generally, Jones and Rakic (2010) concluded that an abnormal number or an improper mix of neurons in a column may arise due to genetic or environmental factors and may contribute to disorders of higher cortical function (e.g.; Buxhoeveden & Casanova, 2002; Casanova & Tillquist, 2008; Gleeson & Walsh, 2000). Thus, we cannot infer if the smaller foot area in SI in persons with BIID is genetically (e.g., congenitally altered) or environmentally modulated (e.g., adapted over years). For the latter cause, Giummarra et al. (2011) suppose that pretending behavior may bring about cortical reorganisation by decreasing or altering sensory information received from the unwanted limbs and resulting in reduced central representation of this limb. For our participants with BIID pretending was indeed rated important (see chapter 2.1.2 for the Zurich BIID Scale and for correlations see p. 91). An abnormal processing in SI, independent of its emergence, might lead to disturbed sensory processes in the affected limbs. However, such anomalies could not be found in our sample as assessed in a standardized neurological examination. Additionally, our participants did not report remarkable or frequent anormal sensations or motor functions of the undesired leg. Thus, we propose that the reduced surface area in SI resulted from back-projected information about an incomplete body image from higher-ordered areas (e.g., right SPL) but sparing sensory and motor limb functions. However, we do not rule out the contribution of peripheral tissue damaged by pretending practices (Giummarra et al., 2011) to a reduced cortical representation of the non-desired limb.

We note a third possible explanation for an altered structure of the smaller area in SI. It may be linked to commonly found sexual components associated to amputation or stumps in BIID (First, 2005). After lower limb amputation it is known that cortical reorganization may lead to erotic sensations in the phantom leg during genital stimulation by micturition or sexual intercourse (referred sensations; Aglioti et al., 1994; Henderson & Smyth, 1948; Ramachandran & Hirstein, 1998). With respect to neuroanatomy, a neighboring region of the foot representation in SI is the genital representation that is located about one cm laterally to the foot (Kell et al., 2005; Michels et al., 2010; Penfield & Rasmussen, 1950). In people with BIID it could have extended and/or invaded into the somatosensory representation of the lower limb. Whether this could have already happen in early ontogenetic life or if the area of

SI could have become smaller through modulation processes is an issue we can only speculate about. Giummarra et al. (2008) assume that such a spatially overlapping and functionally interacting neural mechanism in BIID between sexual arousal and lower limbs could lead to sexual fetishes related to feet or stumps in people with BIID and acrotomophilia. Furthermore, they suggest that such alterations might underlie the desire to amputate the lower limbs. In our sample, erotical components associated with amputation or stumps were rated both as highly for the own body and other persons’ body (see chapter 2.1.2), which would support this hypothesis (for correlations see p. 91). However, it does not explain sexual connotations in a small part of persons with BIID desiring an amputation of the upper limbs. A hypothesis, recently brought-up on the reported sexual attraction of some BIID persons to amputees has been proposed by Ramachandran et al. (2009). Again, these authors suggest that altered cerebral functioning may underlie the sexual inclinations in BIID. They postulate that the innate cortical body image (e.g., represented with a missing leg) would affect limbic circuits of the persons’ brain so that the person develops an ‘aesthetic visual preference’ for amputated bodies. That would explain the sexual affinity for amputees. Beside the presumed genetically driven body image, Ramachandran et al. (2009) do not rule out the possibility of acquired changes in one’s body image. As limbic correlates, they propose the amygdala and nucleus accumbens connected with extrastriate visual areas. We note that our unpredicted findings of a smaller volume in right nucleus accumbens and a trend for a smaller right amygdala in the group with BIID are in line with this hypothesis. However, Oddo et al. (2009) note that so far no study has been conducted to provide evidence linking sexual arousal in BIID and limbic structures. They summarize that in the neuroimaging literature sexual arousal in men mainly activates the thalamus, hypothalamus, amygdala and anterior cingulated cortex (Walter et al., 2008; Karama et al., 2002) as well as the insula and striatum (e.g., Redoute et al., 2000).

Secondary somatosensory cortex (SII)

Another and similar finding of importance is the smaller cortical surface area in the right parietal operculum (OP) in the group with BIID, located in the SII (Brodmann area, BA 43). Studies show that the OP is a polysensory region containing full somatotopic body maps. There, sensory inputs are processed from both sides of the body, even if predominantly by the contralateral body side (Del Gratta et al., 2002; Young et al., 2004; Ruben et al., 2001). The OP is divided into four histologically different areas (OP1 to OP4; Young et al., 2004), with the assumption that each part of the body is represented once in each area (Fink et al., 1997). Stimulation of the hallux revealed contralateral activation in OP1 (ventral part of BA 40) and OP4 (includes BA 43), implicating multiple representations of this body part (Kell et al., 2005; Michels et al., 2010). Comparing our MNI coordinate located in the right OP4 (x = 54, y = -3, z = 9) with that of the left toe activation reported by Kell et al. (2005) (x = 55, y = 2, z = 2) and Michels et al. (2010) (x = 50, y = -2, z = 12) as well as the activation of the left leg of Eickhoff et al. (2007) (x = 57, y = 4, z = 11) it is obvious that we targeted the same area. The smaller right hemispheric foot representation in SII in BIID persons might be linked to an altered recognition and attribution of the foot and finally to its rejection.

SII (especially OP4) is closely connected to areas processing basic sensorimotor information such as SI. Aberrant connections could implicate altered cortical surface in the respective areas. Thus, we suggest three explanations for a smaller area of SI und SII. First, we propose that their altered cortical surface area might reflect a diminished functioning of somatosensory networks. Particularly, back projecting information from connections of higher-ordered areas (for connectivity findings see Eickhoff et al., 2010), such as the right SPL, may have modulated them, by retaining basically spared sensory and motor limb functions.

A second explanation, more from a "bottom-up"-view, focuses on cortical alterations due to regular pretending behavior. This activity is often accompanied by reduced motor and sensory input to cortical areas (Giummarra et al., 2011) and may contribute to or directly cause the smaller cortical surface areas of SI and SII. In favor of this explanation is the fact, mentioned above, that pretending was rated to be important in our sample of people with BIID (Zurich BIID Scale, chapter 2.1.2). However, when we attempted to pursue this proposition, no correlation was found (using Spearman correlation) between the ratings for ‘pretending behavior’ and the individual values of cortical surface area of SI and SII [SI: rho = -0.159, p = 0.603; SII: rho = 0.139, p = 0.649].

A third explanation for the alteration of SI and SII might be related to the pronounced erotic component in BIID. Accordingly, as the foot and genital representation are found to be very closely located in SI and as well in SII (Kell et al., 2005; Michels et al., 2010), a spatially overlapping and functionally interacting neural mechanism could mediate the sexual arousal in BIID (Giummarra et al., 2008; Ramachandran et al., 2009). Our detected smaller cortical surface areas in SI and SII could support such a cortical overlapping. Again, correlating the rated importance of ‘erotic attraction’ of the *Zurich BIID Scale* and the individual values of cortical surface area in SI, did not show a relation [rho = 0.160, p = 0.603]. However, an almost significant correlation (figure 16) was obtained for the rated importance of 'erotic attraction' and the cortical surface area in SII [rho = 0.549, p = 0.052]. To summarize, we find the factor 'erotic attraction' an important aspect of BIID and suggest considering it in future explorations of the functional neuroanatomy of the disorder.

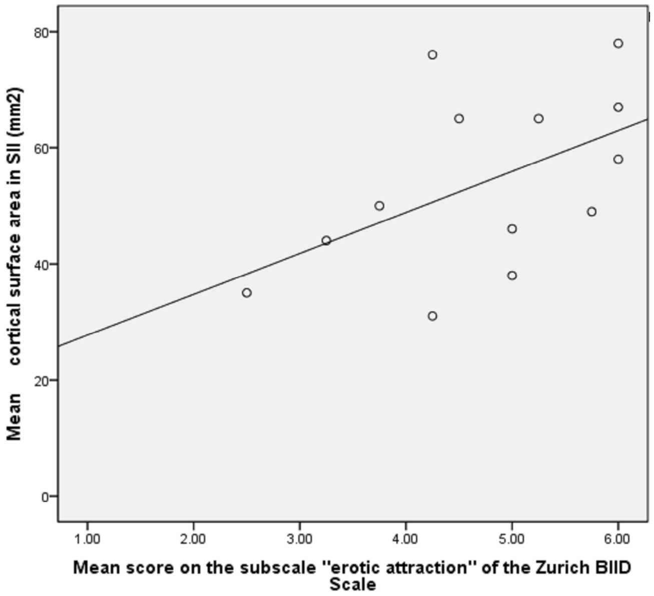


Figure 16: Correlation between individual scores on the subscale 'erotic attraction' of the Zurich BIID Scale (see chapter 2.1.2) and the means of cortical surface area (mm^2).

Superior parietal lobe

We found a thinner cortical area in the SPL in people with BIID compared to control subjects. This finding corresponds with the main result of the first brain imaging study (using MEG) in BIID research. McGeoch et al. (2011) detected an absence of activity in the right SPL to touches in the undesired leg. The authors suggested that the missing activation reflects a disturbed integration of the affected limb(s) in the SPL homunculus that normally contributes to the body image. Our finding of a thinner right SPL in the group with BIID seems likely to be linked to the absence of MEG activation shown by McGeoch et al. (2011) and might support the hypothesis of a specific BIID-related disturbance in right multisensory SPL. In general, such multisensory integration of body-related information includes vision, somatosensation and proprioception that converge in the right SPL, specifically in its posterior part (rPPC; namely in BA 5; Bonda et al., 1995; Lewis, 2006; Wolpert et al., 1998). On the basis of this integration, it is assumed that the right SPL or PPC composes a bilateral representation of the body image (Bisiach et al., 1986; Critchley, 1953; Stein, 1989) and constructs and maintains a sense of self (Longo et al., 2010). From a clinical view, lesions of the SPL, particularly the PPC, may alter higher-order body awareness by causing both negative symptoms (e.g., disownership of body parts as in somatoparaphrenia) and positive symptoms (e.g., supernumerary phantom limbs) (Berlucchi & Aglioti, 1997). The former could be compared to the often assumed conscious disownership of the unwanted limb in BIID (Giummarra et al., 2008). However, besides the PPC, several other brain regions are associated with impaired ownership of body parts, for example the temporal-parietal junction (TPJ) and premotor cortex (for a review see Giummarra et al., 2008).

Altogether, based on clinical evidence and the previous MEG-results by McGeoch et al. (2011), we suggest that our finding of a thinner SPL in the group with BIID is causally linked to the underrepresentation of the particular limbs, leading to the feeling of a disownership of the particular left or right limb and ultimately to a consecutive desire for amputation.

Putamina

At the subcortical level, a further finding of interest was revealed. We found smaller volumes of the left and right putamina in the group with BIID. Again, we assumed that the sensorimotor representation of the unwanted leg in people with BIID is not properly represented in these structures, implicated in the construction of a body map.

The putamen, a nuclueus of the basal ganglia, is primarily associated with sensorimotor coordination and appears to process cognitive functions such as stimulus-response associations and habit learning (Grahn et al., 2008). Focusing on the sensorimotor information, the putamen receives input from SI and supplementary motor areas as well as from SII, which builds the so-called sensorimotor loop (Alexander & Crutcher, 1990). This information has been reported to be somatotopically organized in the putamen in a dorsal to ventro-medial representation of the foot, hand and face area (Gerardin et al., 2003; Leherecy et al., 1998; Maillard et al., 2000; Scholz et al., 2000). Our finding of a smaller volume in both putamina (MNI coordinates, e.g., in the left hemisphere: (x = -32, y = -1, z = 4) is compatible with the findings by Gerardin et al. (2003), who observed an activated region in the posterior part of the putamen upon right foot movements (Talairach coordinates in right hemisphere: x = -33, y = -9, z = 18; and in the left hemisphere: x = -30, y = 0, z = 9).

Furthermore, the coordinates are similar to Ciccarelli et al. (2005) upon right ankle movement (MNI coordinate; x = -30, y = -2, z = 8) and left ankle movement (y = 32, y = -8, z = 4), both reflecting integrative sensorimotor processing. At the subcortical level it is not surprising to find a bilateral result as the body sides are known to be processed in both basal ganglia (Marchand et al., 2008; Scholz et al., 2000). We conclude that our findings in both putamina are located in the foot representation and the smaller volume indicates an underrepresentation of the somatosensory foot information leading to a dysregulation already on this body processing level.

Anterior insular cortex (AIC)

In the right anterior insular cortex (AIC) and adjacent frontal operculum two smaller areas for the group with BIID were shown, whereby the second area did not reach quite our cluster extent threshold of 50 mm^2. Our findings in the right AIC seem to be related to higher cognitive functions, reflecting altered emotional connotations related to the affected limb. The information flow about the affected limb from other brain regions (e.g., SPL) may become emotionally associated and finally conscious in the AIC (reflecting a process we have labeled '*Beseelung*'). To explain this hypothesis in the context of BIID, we first summarize processes related to bodily experience in the insula.

Various studies suggest that the insula is a convergence zone engaged in multiple networks (e.g., see review of Ibañez et al., 2010). Studies suggest that lesions of the right insula may lead to disturbed bodily awareness of limb movement as shown in healthy controls (Farrer et al., 2003), in schizophrenic patients (Farrer et al., 2004) and in patients with anosognosia for hemiparesis or hemiplegia (especially with damage of the right mid-insula; Karnath et al., 2005; Spinazzola et al., 2008). Furthermore, several clinical and experimental studies suggest a crucial role of the right insula in sense of limb ownership, which is dysfunctional in patients with somatoparaphrenia or asomatognosia (Baier & Karnath, 2008; Karnath & Baier, 2010).

The right AIC seems to be associated with intrapersonal perception of stimuli arousing the body (e.g., signals from the body that include heartbeat, pain and touch), a process referred to as interoception (e.g., Craig, 2002; Critchley et al., 2004). The influential model by Craig (2002, 2009, 2010) argues that the AIC is crucial for conscious awareness of all feelings related to the body at one moment. In the AIC a wide range of physiological information about the body such as pain, temperature, sensual touch or visceral sensations are processed and are thought to reach consciousness when a person feels unwell. This homoeostatic internal information on about interoceptive signals pair up with external information (e.g., hot temperature) to form an emotional experience and both states become subjectively aware (e.g., person feels sick standing in the hot sun). Supported by brain imaging studies, Craig (2009) assumes a hierarchical integration of the interoceptive and exteroceptive information in the insula from posterior-to-mid-to-anterior, including environmental, motivational, social and cognitive conditions. Thus, a primary sensory input projected to the posterior insular part would be progressively processed in the middle part of the insula and would reach the highest integrative level in the AIC (Craig, 2009, 2010). The subsequent integration in the insula and its significance for human behavior is thought to optimize energy utilization in an evolutionary context (Craig, 2011).

Our SBM-findings in the right AIC seem to be related to higher cognitive functions, in reflecting emotional bodily states and interoceptive awareness. A similar region in the AIC (MNI coordinates: x = 32, y = 25, z = 9) was described by Critchley et al. (2004), investigating fMRI activity in response to an interoceptive task (judging the timing of own heartbeats). These authors proposed that the right anterior insular/opercular cortex (x = 32, y= 16, z = 10) represents internal bodily states and therefore mediates interoceptive awareness. Further, rather indirect support was presented by Brang et al. (2008), who measured the autonomic arousal using skin conductance response (SCR), in people with BIID by pinpricking the accepted versus undesired leg. SCR is an index of this autonomic arousal and used as an objective measure of conscious and unconscious emotional processing and attention (Damasio, 1994; Frith & Allen, 1983; Ohman & Soares, 1993). Brang et al. (2008) reported heightened SCR below the line of desired amputation and proposed, as mentioned above, that the body image is congenitally not properly represented, which may lead to the anormal sympathetic outflow arguably mediated by the insula. Regions associated with task-independently increased SCR include the right orbitofrontal cortex and right AIC among others (Critchley et al., 2000) and are supposed to mediate the autonomic response reflecting one's own emotional experience of bodily states (Bechara et al., 1997; Critchley, 2002; Oppenheimer et al., 1992).

We link our finding of a smaller right AIC to Brang et al.’ (2008) psychophysiological evidence and hypothesize that the information about an incomplete representation of the affected limb is integrated in the right SPL and modulated by connections to the AIC. Thus, in the AIC discrepant information may converge, composed on one side of signals of the physically present leg and on the other side of impaired information about this leg from other interconnected right hemispheric areas (e.g., SI and SII, SPL and bilateral putamen; Flynn et al., 1999; Mesulam & Mufson, 1985). This might lead to a conscious representation of 'my feelings' about 'that thing' in the AIC (Craig, 2009, 2010). Changes in SCR may be the consequence. For with BIID, a generally increased attention directed to that body part could result, accompanied by a lifelong strong discomfort upon the discrepancy in feelings (cf. also our own findings in a subgroup of persons with BIID; Aoyama et al., in press). In other words, and connecting to Longo et al. (2010), we suggest that impaired body representations are leading to distinct emotional experiences, processed in the AIC, which may reflect the feeling of a missing '*Beseelung'* of the undesired body parts in people with BIID.

Unpredicted finding: Lateral orbitofrontal cortex

An association between BIID and obsessive-compulsive-disorder (OCD) has been discussed in the literature (Braam et al., 2006; Oddo et al., 2009). Patients with OCD have obsessive thoughts leading to repetitive or ritualistic behavior. Similar to that, people with BIID describe to have the enduring wish to be an amputee, what is often accompanied by continuous imagination of the desired body shape or by pretending to be amputated (performed by the vast majority; First, 2005). However, whereas in OCD the thoughts and behaviors are meant to prevent negative outcomes and reduce anxiety, people with BIID do not feel anxious, in contrast, imagining being an amputee usually elicits a (short-lived) feeling of happiness (Oddo et al., 2009). Negative feelings are reported in BIID, if people have no opportunity for pretending (e.g., by lack of anonymity). In this view, a possible compulsive component in avoiding such a negative state could be related to BIID.

Focusing on neural correlates of OCD, a dysfunction of a prefrontal-basal ganglia network has been reported, showing larger grey matter volume in the lateral orbitofrontal cortex (OFC) and the putamen (Menzies et al., 2008a; Rauch et al., 1997; see overview in Rotge et al., 2010). Especially the OFC is thought to rate positive or negative consequences of affected stimuli that contribute to the pathological thoughts and habits in OCD. In contrast, in our data we found a smaller cortical area in the lateral OFC (incidentally, this is the largest cortical difference between both groups in this study) and smaller volumes of both putamina in the group with BIID relative to controls. However, a relation between the individual size of cortical surface area of the lateral OCD and the scores of the OCI questionnaire (obsessive-compulsive traits) from the psychiatric examination could not be found [rho = 0.271, p = 0.371]. This may be due to the rather moderate obsessive compulsive scores in our sample and the restriction of the scattering within the normal range.

Conclusion

Taken together, we propose altered neural networks in BIID both of lower and higher cortical and also of subcortical areas (Blanke et al., 2009; Brang, et al., 2008; Hilti & Brugger, 2010; McGeoch et al., 2011). These networks comprise a diminished leg representation in the right SI and SII cortex as well as in the bilateral putamina. These alterations may lead to a disturbed multisensory information integration of the affected limb in the right SPL and altered emotional feelings, that may be mediated by the AIC (in form of failed '*Beseelung*' of the particular limb). Interactions between these lower- and higher-ordered regions may lead to an incoherent representation of the body. These alterations might result in the feeling of non-belonging of the affected leg and therefore to the desire for amputation. The reported group differences in the structure of specific body related brain areas are suggestive of an underlying neurological deficit and support our main hypothesis proposing that BIID reflects a developmental failure of the embodiment of a physically normally developed limb.

However, we can only speculate about cause-effect relationships regarding the brain morphological differences we found in the present study. Furthermore, even if BIID seems to be related to neurological aspects as shown by our brain anatomical findings and the known phenomenological regularities (e.g., mainly stable amputation location), the structural alterations themselves are unlikely sufficient to explain all clinical observations in their entirety. Rather, a dynamic and integrative perspective, containing psychological and psychiatric components, must be taken to understand the heterogeneity in BIID.

3

General Discussion

Individuals with BIID have the strong feeling that one or more healthy limbs do not belong to their body. To match their physical body to their perceived body identity, they have a longstanding and strong desire to have the non-belonging limbs amputated. Over the past years, there were only a few studies examining the characteristics of BIID (e.g., Blanke et al., 2009; First, 2005; Hilti & Brugger, 2010; Kasten, 2009; Ryan, 2009). These studies show the following ten key observations in BIID: (1) BIID consists of a strong desire for amputation of a limb that is felt as non-belonging. (2) The primary motivation for this amputation desire is to "restore their true bodily identity" (First, 2005, p. 923). (3) The feeling of non-belonging is typically persisting since childhood or adolescence. (4) The desire for amputation bothers the affected individuals strongly. (5) Most people with BIID are men. (6) Legs are vastly favored over arms to be amputated, and the left body side appears to be more frequently affected than the right. (7) Often, there is a specific location for the amputation desire. (8) Sexual preferences are an important component in BIID. (9) Many people with BIID move and behave, as if they were amputated (pretending). (10) BIID is not yet listed in a diagnostic manual, its prevalence and potential treatments are unknown or controversial.

Until recently, there is no consistent opinion about the underlying causes of BIID. Neurological as well as psychiatric causes are discussed (e.g., First, 2005; Hilti & Brugger, 2010; Kasten, 2009). An integrative approach seems to justify the complexity of BIID best (Giummarra et al., 2011).

3.1. Overview on the aims, methods and findings of the present study

In the present study, we hypothesize that BIID has a predominantly neurological basis, rooting in a deficient representation of the undesired limb and/or in a disturbed multisensory integration in cortical and subcortical areas (Blanke et al., 2009; Brang et al., 2008; Hilti & Brugger, 2010; McGeoch et al., 2011). These dysfunctional processes may derange the regular correspondence between the normally developed physical body and the feeling of belonging, what might trigger the amputation desire in individuals with BIID.

Hence, the aim of this thesis was to investigate, whether the unwanted limb in individuals with BIID is misrepresented and/or whether the multisensory information of this unwanted limbs is disrupted. In this respect we particularly envisaged the right parietal lobe and connected brain areas. As far as we know, the present thesis constitutes the first and so far largest experimental study with individuals with BIID and healthy controls. We examined bodily processes on different integration levels using clinical examinations, behavioral experiments and magnetic resonance imaging (MRI; for an overview of the study see table 15).

With respect to behavioral experimentation, up to now no behavioral task capturing the essentials of the condition were known. Our aim was thus to explore BIID with paradigms well-established in the literature on body research and to adapt them to the largely unexplored target stimulus "foot/leg". Note that, if an extremity is the target of present-day experimental research, it is commonly the hand or arm. To prevent side effects of laterality (e.g., judgments for left and right feet) in behavioral experiments we specifically reported findings of homogenous subgroups of people with BIID with a left-leg amputation desire and right handedness/footedness, even if all subjects performed all tasks.

In the following sections our findings for all three kinds of investigations – clinical, behavioral, structural imaging – will be shortly explained and discussed. Corresponding hypotheses, methodological key points and major finding(s) are summarized in table 15.

Table 15: Overview on subjects, hypotheses and findings for all investigations in the study

Chapter	**Investigation**	**Involved multi-sensory information**	**BIID group (within) compared to control group (between)**	**Hypotheses for BIID group**	**Findings**
			Clinical Examinations		
2.2.2	Neuropsychological examination (e.g., attention and memory functions, using paper pencil and computer tasks)		15 subjects with BIID (9 left leg, 2 right leg, 4 both legs) (within) 15 controls (between)	1) No differences 2) Reduced cognitive switching performance (see 2.3.2) in those subjects with BIID, who have enhanced obsessive-compulsive traits in the psychiatric examination	1) Normal cognitive functions in BIID group 2) No reduced cognitive switching performance by the subgroup with obsessive-compulsive traits to an above-median extent No differences between groups
2.2.3	Neurological examination (e.g., sensory and motor functions, including positions sense and vestibular functions)		15 subjects with BIID (9 left leg, 2 right leg, 4 both legs (within) 15 controls (between)	Normal neurological status examination No differences between limb	Normal neurological status examination No differences between limb No differences between groups
2.2.4	Psychiatric examination (e.g., assessing possible psychiatric disturbance or co-morbidities, using interview and questionnaires)		15 subjects with BIID (9 left leg, 2 right leg, 4 both legs (within) 15 controls (between)	1) Normal psychiatric functions 2) Elevated scores in instruments assessing obsessive-compulsive signs	1) Normal psychiatric functions in BIID group 2) No differences in obsessive-compulsive traits No differences between groups

Chapter	**Investigation**	**Involved multi-sensory information**	**BIID group (within) compared to control group (between)**	**Hypotheses for BIID group**	**Findings**
Behavioral experiments (mostly subgroups with homogenous amputation desire and handedness/footedness)					
2.3.1	Mental rotation	Visual, motor, proprio-ceptive (single body parts)	8 subjects with BIID (left leg) (within) Compared to 8 controls (between)	Prolonged RTs for left feet, especially in unnatural positions	No difference between left and right feet in BIID group No difference between groups for feet
2.3.2	Body transformation and task switching	Visual, motor, proprio-ceptive; maybe some emotional aspects (whole body)	7 subjects with BIID (left leg) (within) Compared to 7 controls (between)	1) Faster RTs for figures with a left leg amputation 2) Reduced switching performance in those subjects with enhanced obsessive-compulsive traits	1) No difference between left and right amputated figures in BIID group 2) No reduced cognitive switching performance in BIID (no OCD) 1) Trend for faster RTs to left leg amputation (BIID group compared to control group) 2) BIID group faster switching performance than control group
2.3.3	Rubber foot illusion (RFI)	Visual, tactile, proprio-ceptive	8 subjects with BIID (left leg) (within)	Larger illusion for the left rubber foot in all three measurements, assessing: 1) perceived vividness of illusion (questionnaire) 2) proprioceptive drift 3) skin temperature	1) No difference in perceived vividness of illusion between left and right foot in BIID group 2) No difference in proprioceptive drift between left and right foot in BIID group 3) No difference in skin temperature changes between left and right foot in BIID group.

Chapter	**Investigation**	**Involved multi-sensory information**	**BIID group (within) compared to control group (between)**	**Hypotheses for BIID group**	**Findings**
	[continuation of the Rubber foot illusion (RFI)]		Compared to 8 controls (between)		1) No difference in perceived vividness of illusion between groups for feet 2) Trend for larger proprioceptive drifts in BIID group, but for both feet 3) Trend for larger temperature drop in BIID, but for both feet
2.3.4	Caloric vestibular stimulation (CVS)	Vestibular, spatial, proprio-ceptive	13 subjects with BIID (mixed legs) resp. 8 (left leg) (within) Compared to 13 resp. 8 controls (between)	1) Alleviation of the amputation desire during left-ear CVS 2) Increased skin temperature in the unwanted leg due to 1)	1) No alleviation of the amputation desire 2) No increased skin temperature on the unwanted leg in BIID group of 13 resp. of 8 subjects 2) No relevant group difference of skin temperature change for proximal and distal locations on the legs.
2.3.5	Temporal order judgments (TOJ)	Tactile, temporal, spatial, proprio-ceptive	5 (four left leg and one right leg) (within)	Differential temporal-order integration of touch below and above the desired line of amputation	Faster spatio-temporal integration on unwanted body part (below desired line of amputation) compared to the accepted body part (above desired line of amputation)
			Magnetic resonance imaging (MRI) investigation		
2.4	Surface-based morphometry (cortical thickness, surface area and volume		15 subjects with BIID, (mixed legs) and 15 controls (between)	Focus on right parietal, right insular and subcortical areas known to process low- and high level information about body parts, including legs	Reduced cortical grey matter in: - right SPL (cortical thickness) - right SI, SII and AIC (cortical surface area) - bilateral putamina (subcortical volume)

3.2 Qualitative characteristics of BIID

Besides our main study we gathered data of 53 individuals (including those 15 individuals, who consecutively took part in the study) by an internet questionnaire (chapter 2.1.2). Several of its questions could support characteristics in BIID proposed by previous studies (Blanke et al., 2009; First, 2005). For instance, the amputation desire is present since childhood or early adolescence. Furthermore, 71.7% of individuals with BIID desire a unilateral limb amputation (compared to 55% and 64% in First, 2005 and Blanke et al., 2009, respectively). Moreover, in 77.4% of these persons with a unilateral amputation desire, the left body side was more frequently affected than the right body side (compared to 55% of First, 2005 and to 64% of Blanke et al., 2009). Finally and again according to the literature, the desire to amputate the legs (83%) is more prevalent than that of arms (11.3%). The remaining 5.7% of BIID individuals desired a mixed amputation of legs and arms. With respect to erotic components, we obtained a similar distinct importance in BIID as First (2005; e.g., “If I were amputated, I would experience myself as more erotic”; assessed in the *Zurich BIID Scale*, chapter, 2.1.2). Further, in First (2005), as well as in our questionnaire approach, the most important reason for the amputation desire turned out to be the discrepant feeling between physical body and body identity (e.g., “I would feel myself more "complete" after the desired amputation”).

3.3 Individuals with BIID show normal neuropsychological, neurological and psychiatric functions - and BIID is not likely to be associated with OCD

In the clinical examinations we found the following results. First, as predicted, normal neuropsychological functioning was shown (e.g., normal attention or memory functions). Second, also neurological functioning as revealed in our standardized neurological examination (e.g., normal sensitivity or reflexes) was ascertained. This finding is in line with Brang et al. (2009) and McGeoch et al. (2011). Third, our comprehensive psychiatric examination showed that BIID individuals and controls did not differ with respect to any psychiatric disorders, i.e., there were, among others, no elevated signs of psychosis, depressive, anxious and stress symptoms in neither subject group. Also this finding is in accordance with the findings of previous studies (First, 2005; Kasten et al., 2009; Thiel et al., 2009).

However, against our prediction, individuals with BIID did not show elevated obsessive-compulsive signs (not even a trend, as described by Thiel et al., 2009). Raw scores on the psychiatric rating scale (OCI) were not significantly related to switching performance in one of the behavioral tasks ("body transformation and switching task", chapter 2.3.2), but only to the performance in one out of four selected neuropsychological tasks (chapter 2.2.2). Hence, our results speak against a prominent association between BIID and obsessive-compulsive traits. Our MRI investigation is compatible with this conclusion, insofar as we found a *smaller* cortical surface area in the lateral OFC and *smaller* volumes of both putamina in the BIID group relative to the control group. This is in contrast to previous studies proposing that the neural correlates of OCD seem to be *larger* grey matter volumes in the lateral orbito frontal cortex (OFC) and the putamen (e.g., Rotge et al., 2010).

3.4 BIID is likely to be associated with specific neurological alterations

Our main hypothesis proposes that the felt discrepancy between the physical body and body identity in BIID may be mediated by disturbed neurological functions, i.e., representations and/or multisensory integration. The behavioral experiment of temporal order judgments (TOJ) and the brain imaging investigation (MRI) support the assumption that BIID is accompanied by alterations of the right hemispheric SPL, SI, SII and AIC, as well as the bilateral putamina.

3.4.1 Defective spatio-temporal integration in BIID (TOJ)

Our first important finding supporting our main hypothesis, is a first-ever evidence for a psychophysiological correlate of BIID. In the behavioral experiment using TOJ (Aoyama, et al., in press) a subgroup of five individuals with BIID with a unilateral amputation desire had to rate which of two tactile stimuli was applied first to the proximal and distal site of their stable desired amputation line ("demarcation line"). As predicted, we could find different TOJ, i.e., participants prioritized the tap on the distal, unwanted part, over that on the more proximal, accepted part of the leg. Thus, the spatio-temporal integration was biased towards the undesired body part. Conversely, on the control leg (only accepted body parts) there was a significant prioritization of the proximal site. This is most probably in accordance with the shorter neural transmission times for proximal as compared to distal stimulation sites.

The finding, that a body part, which is not accepted as an integral part of one's self, needs to be stimulated *after* that of a fully integrated part in order to generate the experience of simultaneity, is interesting. Usually, affected sensory fields need to be stimulated *before* their unaffected counterparts in TOJ experiments. For instance, tactile TOJ in patients with complex regional pain syndrome prioritize the unaffected before the painful side (Moseley et al., 2009). While these patients have sensory impairment, our participants, in contrast, do not complain about sensory deficits and none have been assessed in the neurological examination. Thus, we tentatively propose that the shown prioritization of an undesired part of the body is due to a *hyperattention* directed towards that part. This *hyperattention* is reminiscent, on the level of a hemibody, of the syndrome of *acute hemiconcern* after specifically right parietal lesions (Bogousslavsky et al., 1995). Our findings in the TOJ experiment support that BIID may root in neuronal dysfunction. We agree with Brang et al. (2008) and McGeoch et al. (2011) to envisage the right parietal lobule and its connections with the insula as altered underlying networks in BIID.

3.4.2 Altered networks for processing low- and high-level body information (MRI)

Our second important finding was discovered using MRI. This is the first study to gain insight into the structural neuroarchitecture of BIID. Using surface-based morphometry, we examined gray matter differences in cortical thickness, surface area and volume between individuals with BIID and healthy controls. We focused on differences in right parietal, insular and subcortical areas (Blanke et al., 2009; Brang et al., 2008; McGeoch et al., 2011) that are thought to process information about body parts and emotional connotations likely to be implicated in BIID. As predicted, we found decreased cortical thickness in the right superior parietal lobe (SPL) in BIID. This finding is in line with the recent results by McGeoch et al. (2011), who showed a less activated SPL in their MEG study upon touch of the undesired limb compared to touch of the accepted limb. Moreover, in the BIID group also a reduced cortical surface area in the right primary and secondary somatosensory cortex (SI, SII) and in the right anterior insula (AIC; see the speculations by Brang et al., 2008; McGeoch et al., 2011) were shown. Furthermore, our findings revealed a reduced volume in bilateral putamina. We suggest that these findings represent altered networks for processing both low-level sensory information and higher-order body-related functions. These networks are proposed to comprise (1) a diminished leg representation in the right SI, SII and in both putamina, (2) a disturbed multisensory integration of the affected limb in the right SPL and

(3) altered mediation of emotional connotations of the affected limb in the right AIC. Together, we argue that these alterations might lead to the feeling of non-belonging of the affected leg and therefore to the desire for healthy limb amputation.

Whereas altered right SPL and insular cortex functions in BIID have already been proposed (Brang et al., 2008; McGeoch et al., 2011), our findings of significantly smaller SI and SII areas are novel and unprecedented. This raises the question as to the way in which these regions contribute to BIID. Smaller areas in SI and SII seem to be located at the place where the foot or the leg is represented. Hence, an alteration, especially in SI, would primarily be associated with diminished sensory and motor limb functions. However, individuals with BIID reported normal sensory functioning of the unwanted limb and were also shown to have normal neurological functions in our clinical examination. In chapter 2.4 three possible explanations are discussed. We conclude that our first explanation, i.e., a cortical modulation of SI and SII by faulty back-projections from higher-ordered areas, may be a major determinant. Note that we obtained data on structural peculiarities in such higher-order areas (e.g., right SPL). Additionally, the often reported pretending behavior as well as the prominent erotic components in BIID might be also be candidates likely involved in the cortical reorganisation from childhood over the whole life span (see chapter 2.4, p. 91 for more detail).

3.4.3 Linking defective spatio-temporal integration (TOJ) to neuronal correlates of BIID

The structural-neurological alterations found in our MRI approach may be associated to the defective spatio-temporal integration on the unwanted limb, as reflected in the TOJ experiment. It is known that TOJ are mediated by several brain areas, including bilateral SII, posterior parietal cortex, right AIC, inferior frontal cortex and subcortical regions, as the basal ganglia and cerebellum (Lacruz et al., 1991; Pastor et al., 2004). Thus, a hypothetical model for the defective spatio-temporal integration might include the right SPL (reduced cortical thickness; SPL is a part of the posterior parietal cortex). This right SPL was recently proposed to have a misrepresentation of the critical limb (e.g., McGeoch et al., 2011). This may lead to a differential integratation of tactile information from below and from above the demarcation line (TOJ: faster from the unwanted limb segment) in the right SPL. The information from the legs is sent to the SPL via lower level areas, as the right SII (MRI: smaller cortical surface area) and the putamina (MRI: reduced cortical volume). A role of the SII in TOJ may be to process attentional modulation of sensory inputs (e.g., Inui et al., 2004; Mima et al., 1998;

Steinmetz, Roy et al., 2000). The spatio-temporal information concerning the limb finally combined in the right SPL may be forwarded to the right insula (Brang et al., 2008). There, a conscious and higher-ordered attention process may emerge in the anterior insula (MRI: smaller cortical surface area; Craig, 2002, 2009). We assume that this process leads to a generally exaggerated attention to the body part may, on the clinical level, even suggest an obsessive-compulsive like behavioral preoccupation. This process of a hyperattention may be the behavioral correlate of the heightened SCR (predominantly mediated by the right insula) shown by Brang et al. (2008) upon touch of the unwanted limb. Taken together, our results suggest that the physical presence of the unwanted limb might be a source of continuous attraction of attention and the feeling of being "overcomplete" in people with BIID (Aoyama et al., under review). To investigate the proposed altered neural tracts between right parietal lobe and the right AIC, tractography will be performed from our MRI data.

3.5 Behavioral experimentation in BIID: The role of the tactile modality

With various behavioral experiments, we specifically aimed to assess multisensory information integration in the right parietal cortex and connected brain areas that are expected to be altered specifically for the undesired leg. In an explorative manner we aimed to explore BIID with known paradigms used in body research and adapted them specifically to explore legs and feet. However, we obtained several null results or only small trends in the four behavioral experiments discussed in this section. This implicates that, contrary to our prediction, the unwanted and the accepted foot did not differ from each other in these experiments. Possible explanations for the null findings will be described in the following paragraphs.

It has to be noted first that a limitation of our study may be the small number of participants to detect the hypothesized differences – even if it is so far the largest experimental study ever performed to explore possible behavioral correlates of BIID. To reduce statistical noise, we especially analyzed data of homogenous subgroups with a left-sided leg amputation desire and right handedness/footedness (see table 15)

First, performance in the *mental limb rotation task* is thought to require integration of visual, motor and spatial information. Therefore, we assumed that mental rotation ability may be specifically reduced for the unwanted foot. However, we failed to detect prolonged reaction times for the unwanted foot in individuals with BIID with a left-sided amputation desire.

Presumably, a mental rotation tasks with a higher demanding level (e.g., more complex biomechanical postures) could have been more qualified to detect differences between unwanted and accepted limbs in BIID. According to Curtze et al. (2010), who also failed to show laterality effects of feet (in this study, in unilateral amputees) in a similar mental rotation task, participants may have solved the task on a more abstract knowledge than referring to a representation of the own one-legged body. We join these authors in their conclusion and propose that future experimentation should include functional imaging during mental rotation performance. The SPL, intraparietal sulcus, inferior parietal lobe and premotor cortex seem to be activated (Bonda et al., 1995; Kosslyn et al., 1998; Parsons, 1994; Shenton et al., 2004). As we only found the right SPL and the inferior parietal lobule to be altered in our MRI investigation, the structural findings, if implicated in mental limb rotation at all, may show too less anatomical overlap with those structures previously described as crucial for mental rotation ability. We favor to speculate that a task involving additional tactile information or more emotional task demands might be better qualified to discover differences of multisensory integration of the unwanted limb in BIID.

The following task, also thought to involve visual-motor integration (but still not delivering tactile information) might be retrospectively better suitable to discover differences, as it involves a whole body shape, instead of single body parts. This might evoke more attentional and/or emotional mechanisms (e.g., as processed by the AIC). Thus, in the *body transformation and switching task* subjects had to decide whether a depicted figure was left- or right-leg amputated. For the group with BIID with a left-sided leg amputation desire we expected faster RTs for those displays with a left-sided leg amputation (due to the compatibility of seen and felt deficit). However, our hypothesis could not be verified when comparing the RTs for left and right-sided amputation figures within the group of BIID. Nevertheless, when comparing the BIID group with the control group, a trend for faster processing of the desired left-leg amputated body shape for persons with BIID was shown. Thus, we are somewhat reluctant to entirely exclude facilitated mental perspective transformation abilities in BIID. Such facilitation might be due to a lifelong mental imagery of a specific body shape or due to real experiences of oneself in the desired body shape during pretending. Even an early ontogenetic under-representation of body-related brain processes in temporo-parietal regions cannot be excluded to have played a role in this process. Our results fell short of significance and we emphasize that our analyses rely on simple performance means and that did not comprise analyses for capturing characteristics of underlying RT distributions (see e.g., Balota & Yap, 2011).

Third, to examine the hypothesized altered multisensory integration, specifically for visual, tactile and proprioceptive information, we used the paradigm of the *rubber foot illusion (RFI)*. In this experiment the unseen foot of the subjects was stroked while they had to watch a rubber foot that was simultaneously stroked. Thereby an illusion may arise that consists in the feeling that the rubber foot belongs to oneself (Botnivick & Cohen, 1998). We predicted an elevated RFI for the rubber foot that corresponded to the unwanted foot compared to the accepted foot in people with BIID, due to their hypothesized altered multisensory integration (Giummarra, et al., 2011). We quantified the size of the illusion by three measurements comprising (1) the subjectively reported vividness of the illusion by means of a questionnaire, (2) proprioceptive drift, and (3) skin temperature (Botnivick & Cohen, 1998; Moseley et al., 2008; Tsakiris & Haggard, 2005). However, and in contrast to our hypothesis, the findings according to all three measurements suggest that in persons with BIID, the size of illusion for the unwanted foot was not significantly increased. Trends for a larger proprioceptive drift and larger temperature drops were shown in persons with BIID compared to controls, however they were obtained for both feet. They indicate, if anything, a generally elevated RFI susceptibility for people with BIID, but no asymmetric RFI due to unilateral BIID. Thus, as comparable visuo-tactile-proprioceptive integration in people with BIID in both feet was found, our hypothesis of an altered integration of multisensory information of the affected foot has to be rejected. This result is somehow disappointing, as tactile information is included in RFI, what we now proposed to be more promising for detecting multisensory alterations in BIID. The null finding may be explained by our MRI findings. With respect for corresponding brain areas activated by the RHI (e.g., Ehrsson et al., 2004; no imaging data exist for RFI) only one altered brain area, the unpredicted inferior parietal lobe, is thought to be common in both. Thus, the neural basis of the RHI that has been especially related to activity in bilateral premotor cortex and the inferior parietal lobe might not be reflected in the structural differences we describe in the present investigation.

Finally, the fourth behavioral experiment leading to a null finding was the *caloric vestibular stimulation (CVS).* Here, participants’ external ear canals were stimulated with cold water while they had to rate the actual "feeling of disturbance" for all four limbs. We predicted that cold water CVS of the left ear temporarily alleviates the desire for limb amputation in BIID

(Ramachandran & McGeoch, 2007b) and an increase in skin temperature in the affected limb will consequently be shown (Moseley et al., 2008). The method might thus stimulate the hypothesized interrupted multisensory integration in people with BIID. In contrast to our prediction, persons with BIID reported no alleviation of the amputation desire during cold-water CVS of either ear. Furthermore, CVS did not induce a significant change in temperature of the undesired limbs in the BIID. Our null findings discourage the usefulness of the procedure to alleviate the desire for limb amputation in persons with BIID. CVS has been shown to induce activation in the posterior insula, intraparietal sulcus, superior temporal gyrus, hippocampus, cingulate gyrus and thalamus (Suzuki et al., 2001). This broad activation comprises a large cortical surface area and could theoretically be related to some of the unpredicted areas of structural differences we found between persons with BIID and controls. However, we again emphasize that any comparisons between assumed structural correlates of BIID and brain areas activated during functional neuroimaging are almost certainly premature.

In sum, we failed to detect differences between the undesired and the accepted limb in people with BIID in four out of five behavioral experiments. The positive findings in the TOJ experiment (Aoyama et al., in press) fit in nicely with the findings by Brang et al. (2008) using SCR. Some of the tendencies we found in, for instance, the body transformation and switching task may seem promising. We support that future research should not abandon the way we have initially paved, but perhaps add functional imaging in combination with some selected paradigms.

4

Conclusion

We aimed to investigate, whether the unwanted limb in individuals with BIID is misrepresented and/or whether the multisensory information about this unwanted limbs may be disrupted at some integration stage. In this study with BIID, so far the largest ever conducted, we used clinical examinations, behavioral experiments and magnetic resonance imaging.

We compared previous, more anecdotal findings regarding key characteristics in BIID with the data of our internet questionnaire of so far 53 people with BIID. Here, we could support characteristics found to be prominent in BIID, as for instance, type and side of the desired limb to be amputated, subjective notions about the reasons for the amputation desire and the importance of erotic components in this identity disorder still largely enshrouded in mystery.

First, in the clinical examinations we found normal neuropsychological, neurological and psychiatric functions in persons with BIID. Specifically, our results of the psychiatric examination propose that BIID, in our sample, was not associated with pronounced obsessive-compulsive traits. Taken together, the underlying causes of the feeling of non-belonging respectively the desire for amputation in people with BIID do not seem to be captured by today's standards of clinical examination.

Second, we found that BIID is likely to be associated with specific neurological alterations. Thus, while four behavioral experiments gave null results (see 3.5), in one behavioral experiment we uncovered an apparently disturbed temporo-spatial integration of tactile information in the unwanted limb (TOJ experiment). Another major finding was obtained by MRI investigations showing brain morphological differences of the grey matter of specific brain areas, namely in the right SPL, right SI and SII, right AIC and both putamina between groups. The observed differences may indicate altered networks for processing both low-level sensory information and higher-order body-related integrative functions. We infer that the differences might lead to the feeling of non-belonging of the affected leg and therefore to the desire for a healthy limb amputation. By linking our findings of the TOJ to those of the MRI experiment, we propose a model includes a hypothetically altered multisensory integration in the right SPL (due to a misrepresentation of the leg). In the right SPL, the tactile information from below and above the demarcation line in people with BIID might be differently integrated (faster integration for the unwanted, distal part). Via interconnections with the right SII and the putamina the information of altered leg representations may be combined in the right SPL and fail to provide a normal signal to the right insula. There, the altered information may come to awareness, but in a rather distorted way, i.e., resulting in a continuous feeling of being "overcomplete" and a generally exaggerated attention to that body part in persons with BIID.

The neurological underpinnings pointed out by the present investigation are certainly in need to be elaborated on in further research. An integrative approach seems in need to justify the complexity of BIID. With regard to the many open questions and obscurities still surrounding BIID, follow-up studies should aim to elucidate how the body incongruity under investigation could be further explored, taking into consideration an integrative approach. Moreover, examining particular therapeutic approaches, as well as empirical studies with post-amputated people with BIID would help enable individuals with BIID to live a life with reduced suffering. Possible therapeutic approaches include repetitive transcranial magnetic stimulation, transcranial direct current stimulation or, on a more invasive side, deep brain stimulation. All these methods might alter the hypothetically disturbed multisensory integration of the undesired body parts in people with BIID and circumvent the last-resort solution, i.e., limb amputation.

5

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6

Curriculum Vitae

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Education

10/2008 - 10/2011	PhD in Psychology, University of Zurich International PhD Program in Neuroscience, Neuroscience Centre Zurich, ZNZ
10/2002 - 03/2008	Licentiate of Psychology, University of Berne
08/1997 - 06/2002	Primary School Teacher Diploma, Teachers’ college Bernarda, Menzingen

Employments

01/2008 - 10/2011	Clinical Assistant in Neuropsychology, Neuropsychological Unit, Neurology, University Hospital Zurich
	Clinical Traineeship for Neuropsychology
03 - 06/2008	Citizen Hospital, Solothurn (100%)
11/2006 - 01/2007	State Hospital Rankweil, Austria (40%)

	Research Trainee in Psychology of Perception
09 - 10/2006	Centre Européen des Sciences du Goût, Dijon, France (100%)
08 - 10/2005	Institute of Food, Nutrition and Health, ETH Zurich (100%)
08/1999 - 06/2002	Primary Teacher in Education (in total 6 month)

List of publications

Publications in peer-reviewed periodicals

Aoyama, A., Krummenacher, P., Palla, A., Hilti, L. M., & Brugger, P. (in press). *Impaired spatial-temporal integration of touch in body integrity identity disorder (BIID).* Spatial Cognition and Computation.

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Vitacco, D. A., Hilti, L. M., & Brugger, P. (2009). Negative Phantom Limbs? A Neurological Account of Body Integrity Identity Disorder. In: A. Stirn, A. Thiel, S. Oddo (Eds.). Body Integrity Identity Disorder: Psychological, Neurobiological, Ethical and Legal Aspects. Lengerich*: Pabst Science Publishers, p. 201-210.*

Publication in preparation

Hilti, L. M., Vitacco, D. A., Hänggi, J., Krämer, B., Palla, A., Luechinger, R., Jäncke, L., & Brugger, P. (in preparation). *Desire for healthy limb amputation: structural brain correlates*.

Poster presentations

Aoyama, A., Krummenacher, P., Palla, A., Hilti, L. M. & Brugger, P., (2011). *Impaired tactile temporal order judgements in body integrity identity disorder.* European Workshop on Cognitive Neuropsychology, Bressanone.

Hilti, L. M., Vitacco, D. A., Hänggi, J., Krämer, B., Palla, A., Luechinger, R., Jäncke, L., & Brugger, P. (2011). *Desire for healthy limb amputation: structural brain correlates*. 3rd Scientific Meeting of the European Societies of Neuropsychology (ESN), Basel.

Hilti, L. M., Tamagni, C., Palla, A. & Brugger, P., (2010). *Amputation desire: no alleviation by caloric vestibular stimulation.* 40th Annual Meeting of Society for Neuroscience, San Diego.

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